Pharmacology

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Name: _____

Subject: **Pharmacology**

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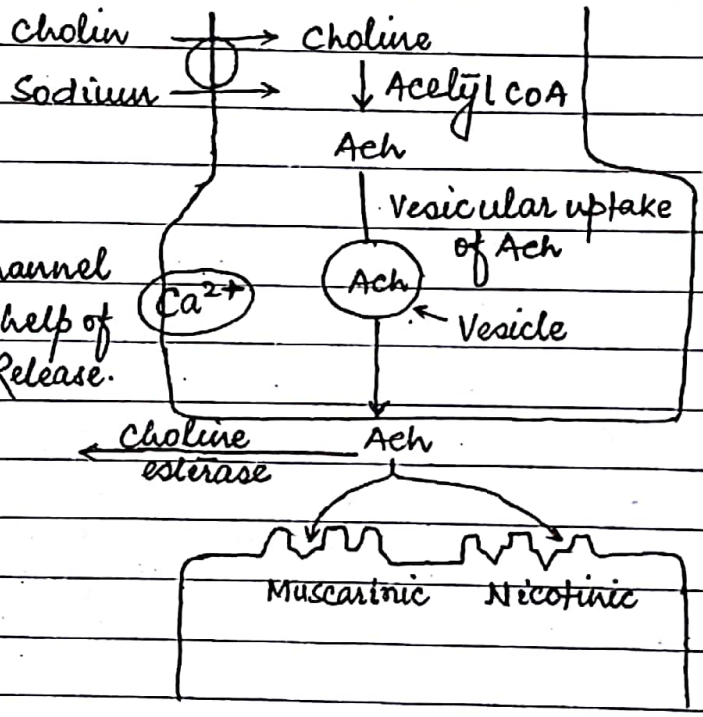
PHARMACOLOGY

- Sympathetic System Neurotransmitter – Nor-Epinephrine
  ↳ Thoraco lumbar outflow (T_1 to L_3)
- Parasympathetic System Neurotransmitter – Acetyl choline
  ↳ Cranio-sacral outflow (III, IV, IX, X, S_2, S_3, S_4)

Cholinergic drug:

Choline uptake – Na^+-choline Symport
↳ 1st step → Rate limiting step in synthesis of Ach.

Source of choline → Serine.



True cholinesterase → +nt at synapse.
Pseudocholinesterase → +nt in plasma.
Cholinergic drug —metabolised by→ Pseudocholinesterase.
Choline uptake inhibited by → Hemicholinium.
Vesicular uptake up of Ach blocked by → Vesamicol.
Release of Ach modulated by < Blocked by – Botulinum toxin
Stimulated by – Spider Venom.
Defect in Ca^{2+} Channel – Lambert Eaton Syndrome.

Lambert Ealon Syndrome:
Defect is Ca^{2+} channel Presynaptically.
For t/t we need Ca^{2+} channel activator → 3,4-diamino pyridine
(Dalf Ampridine)
↓
Also useful for t/t of
- Multiple Sclerosis
to improve walking capacity.
- It is K^+ channel blocker & Ca^{2+} channel activator.

Sites of Release of Ach Neurotransmitter:
at the ① Ganglion
- Preganglionic fibre of sympathetic & parasympathetic Release Ach at ganglion.
② Adrenal Medulla.
③ Neuromuscular junction.
④ Postganglionic Parasympathetic fibre.

Postganglionic sympathetic fibre normally releases
- Nor-epinephrine (NE)

Exception:
a) Sweat gland - Release Ach (Sympathetic cholinergic)
Hyperhydrosis (Excessive Sweating)
↓
t/t < Sympathectomy
Botulinum toxin injection.
b) Renal blood flow :- Release Dopamine by Sympathetic postganglionic fibre.

Extra point:

① Conversion of NA into Adrenaline by Methylation
- Eg. of Phase II reaction.

② Conversion of Histamine into methyl histamine by Methylation.

Mast cell secrete histamine.

- Mastocytosis (Histamine releasing Tumour)

↓

urinary estimation of Methyl histamine - Useful for diagnosis of Mastocytosis.

Urinary estimation of VMA (Vanilyl Mandelic Acid) - Useful for diagnosis of Pheochromocytoma.

Toxins in ANS:

BOTULINIUM TOXIN — A to G Subtype.

Clinical uses of Botulinum A toxin:

① Blepharospasm
② Strabismus
③ Wrinkle (in forhead corrected)
④ Cosmetics.

Clinical uses of Botulinum B toxin:

- Used as Muscle relaxant.
  ↳ Cervical dystonia (Painful muscle spasm)

ONABOTULINUM TOXIN

- Derivative of Botilinum A toxin.

Useful for — ① Prophylaxis of Chronic Migraine.
② Relaxation of Detrussor muscle - Given intra vesically.

↓

Causing Retention of urine
So useful for t/t of overactive bladder.

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Alpha Bungarolōxin:

- Component of Venom of Banded Krait

Nature of toxin — Antagonistic action at N_M receptor.

Saxitoxin, Tetradoxin — Both released by Dinoflagellates (Algae)

↓

This toxin infect a fish (shell fish)

↓

Ingested by human — cause Na^+ channel blockage, causing Muscle Paralysis.

So, called Paralytic shell fish poisoning.

T/t of α-Bungarolōxin:

Neostigmine & Atropine

↓

↑ Ach in synapse

Action

Muscarinic — Nicotinic

↑⊖

Atropine

- We need only nicotinic action, we don't need muscarinic action.

So, muscarinic blocker given.

Cholinoceptors.

Muscarinic	Nicotinic
- M_1, M_2, M_3, M_4, M_5	N_M, N_N
- All muscarinic are G-coupled protein receptor.	- All nicotinic are ligand gated.
- Acting via	

Adenyl cyclase pathway
- G_s → Stimulatory
- G_i → Inhibitory

Phospholipase pathway
2 imp. 2nd Messenger: IP_3, DAG.

Adenylcyclase Pathway:
2nd Messenger — CAMP.
M1, M3 & M5 follow Gq pathway
M2 & M4 follow Gi pathway.

Muscarinic Receptors:
M1 : Location – Stomach
Action – Releasing HCl
Overstimulation of M1 – Gastritis
Selective M1 agonist – Oxotremorine.
↳ GE – Gastritis
For Gastric ulcer – Block M1.
Selective M1 antagonist < PIRENZEPINE > For t/t of gastric ulcer.
TELENZEPINE

M2 : Located on Myocardium
↳ Maximally in AV node.
Action : Stimulation of M2 causes reduction in conduction velocity.
↓
Causing Bradycardia
as Vagus (X) fibre is Parasympathetic fibre
↳ act on M2 receptor → Causes Bradycardia.
Athletic person → High Vagal tone
Vagomimetic drug → Causing Bradycardia
Use of M2 agonist → SVT (Supraventricular Tachycardia).
Selective M2 agonist – METHACHOLINE < 98-99% – M2 (Action)
1-2% – M1, M3
Selective M2 antagonist – METHOCTRAMINE
TRIPITRAMINE
Methacholine challange test → Δ of Asthma.
↳ Cause bronchoconstriction.

Digoxin = Vagomimetic property
- Anti-arrythmic
  Atrial Fibrillation
  Atrial flutter.
- Inhibit $Na^+ - K^+$ ATPase test.
- Accumulate intracellular Ca^{2+} ($\uparrow Ca^{2+}$)
- ↑ Force of contraction
- Useful for t/t of low output CCF.

Muscarinic Receptors:

M_3 Receptor — Location:
- Smooth muscle — Blood vessel (endothelium)
- Eye
- Endocrine glands.

Smooth muscle

Vascular	Visceral
– Endothelium	– M_3 antagonist – (COPD / BA)
↓	• Ipratropium bromide
Vasodilation	• Thiotropium bromide.
Hypotension	We don't use Atropine bcoz
	– Selectivity.
	• Don't interfere muco ciliary muscle.
	– Intestine & Bladder
	• Pro-kinetic action

M_3 agonist: Uses
- Constipation
- Post op paralytic
- ileus, urinary retention.

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Selective M_3 agonist acting on Intestine & Bladder
→ BETHANECHOL

Selective M_3 agonist acting on GIT & Bladder
- DARIFENACIN
- SOLIFENACIN
- useful for t/t of diarrhoea & diarrhoeal dominant IBS.
Over acting bladder.

Selective M_3 agonist acting only on Bladder
- Vesico selective M_3 agonist.
  - Oxybutynin
  - Flavoxate
  - Tolterodine
  - Fesoterodine (Prodrug)
  - Trospium chloride.

Active form

Extra information on bladder:
β_3 Action - Relax detrusor - causing urinary Retention
↓
MIRABEGRON (β_3 agonist)
↳ Use - Overactive bladder.

Location of β_3 mostly in adipose tissue
- SIBUTRAMINE (β_3 agonist)
  - Adipolysis (wt. loss)
- It is withdrawn - Bcoz Cardiotoxic.

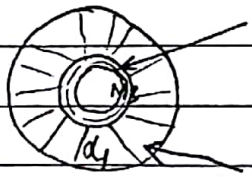
Nocturnal enuresis
- Imipramine (TCA)
  - Anticholinergic

DOC : Desmopressin
V_2 analogue - Vasopressin

Stress incontinance :
t/t → Duloxeline
- ↑ urethral tone
- also useful for t/t
  - Chronic neuropathy pain
  - Fibromyalgia.

- It is SNRI (Anti-depressants)
  ↓
  eg: Duloxeline
  Venlafaxine (S/E - Sustained HTN)
  Milnacipram
  Leva-milnacipram
  Vilazodone
  Vortioxetine] Newer drug.

M_3 on Eye :



Sphincter muscle
Constrictor
Stimulation of M_3
- Constriction of pupil
(Miosis)

Radial muscle
Dilator
Stimulation of d_1 :
- Mydriasis
  ↳ On Radial muscle.

M_3 agonist acting on eyes
- Pilocarpine
- Ecothiophate
  - Organophosphorus Compd
    Irreversible cholinesterase inhibitor

α_1 agonist acting on eyes:
- Phenylephrine
(Adrenergic agonist)

Adrenergic drugs – Only Mydriasis

Anticholinergic drugs – Mydriasis + Cycloplegia
(loss of light reflex)

β-blocker don't alter pupil size
Timolol – Use in t/t of Glaucoma.

Oculomotor Nerve supplies constrictor muscle.
(Circular muscle).

Causes Miosis.
Injury – Mydriasis
Even after CN III nerve injury if we use pilocarpine we will get miosis, as receptors are intact.

M_3 ~~receptor~~ agonist – Useful for glaucoma.
Pilocarpine – Useful for glaucoma by promoting drainage
Ecothiophate – S/E – Cataract.

Mydriatic anticholinergic:
Atropine (longest acting = 1wk)
Homatropine
Cyclopentolate
(M/C) Tropicamide (Fastest but shortest acting = 3-6hr)

↳ C/I – Glaucoma.

Only for fundus exam – Mydriasis enough
↓
Phenylephrine prefferred
(OR)
Tropicamide.

Error of Refraction:
• Mydriasis & Cycloplegia
DOC – Tropicamide

• In child < 5yr
• Atropine Ointment 1%

M_3 on exocrine glands:
M_3 location – Salivary gland
Lacrimal gland
Sweat gland.

M_3 agonist : Pilocarpine
Cevimeline

Sjogren syndrome – Pilocarpine used
Xerostomia

Amifostine – Radioprotective
↓
Antidote for Cisplatin
↳ S/E – Nephrotoxicity.

Radiosensitizer – Gemcitabine, Metronidazole.
Radiation Recall – Dactinomycin, Doxorubicin
Anticancer antibodies

Gemcitabine :

Pyramidine anti-metabolite

DOC - Pancreatic Cancer.

Atropine — C/I in hyperthermia

Nicotinic Receptors :

Nm & Nn

Nm :

N = Nicotinic , m = Skeletal muscle

① Activation of Nm causes opening of Na^+ & Ca^{2+} channel.
Entry of Ca^{2+} causes contraction of muscle.
(Muscle depolarisation)

Ach — ↑ muscle power
So, cholinergic drugs used for t/t for Myasthenia gravis.

Skeletal muscle Relaxation (SMR) :

d - Tubocurarine = Competitive antagonist.
↳ Non depolarising SMR.
For reversal — Neostigmine
c Atropine

Newer drug — Sugammadex
↓
Useful for Reversal of Rocuronium & Vecuronium.
• Similar to Neostigmine

Non-depolarizing SMR

Steroidal — Non-Steroidal (Benzyl isoquinoline)

Pancronium, Rocuronium, Rapacuronium, Vecuronium

Pancronium → Anticholinergic action (or) Anti Vagal.

Glycopyrolate : Anticholinergic agent
Useful for pre anaesthetic medication to control Secretion.
It is quaternary compd — lipid insoluble,
So, NO CNS side effect. So it is useful instead of Atropine.

Rocuronium :
- Fastest acting SMR
- Alternate to Succinyl choline (Sch) for Tracheal intubation
- Least histamine releasing property.
- Severe pain during injection

Rapacuronium :
- Cause Severe Bronchospasm.

Vecuronium :
- Preferred in cardiac pts.

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Benzyl isoquinoline

Doxacurium
- longest acting (120min)
- Most potent.

Mivacurium
- Shortest acting (15-21 min)
- Useful for day care Sx.

Gantacurium
(5-10 min)
↓
Newer drug.

Atracurium
- Undergoes Hoffman's degradation (Self metabolism)
↓
metabolism out liver & kidney.
They do not need enzyme for degradation
- Safe in Hepatic/ Renal failure
- Produce by product
↓
Laudanosine
(Causes - Seizure)

d-Tubocurarine
- Max^{m} Histamine Releasing
- Adverse effect
  - Bronchospasm
  - Hypotension.

Cis Atracurium — Less laudanosine
Less secreting histamine.

SMR having less histamine releasing property
- Cis. Atracurium
- Rocuronium.

Depolarising SMR:

Succinyl choline (Sch):

Structurally & functionally ~~—~~ similar to Ach.

S/E – Muscle fasciculation
Post op. muscle pain

- Shortest acting (3-5 min)
rapidly undergo metabolism by Pseudocholine esterase.

Some people have Atypical Pseudocholine esterase
↑ action < 5 min
Lead to Sch Apnoea
T/t – Fresh blood transfusion bcoz blood plasma is rich in pseudocholine esterase.

Dubucaine number:

Useful to access whether the pt. have atypical pseudocholinestrase or normal.

Caine – Local anesthetic agent.
80% – hydrolysis – Normal Pseudocholinesterase.
<20% – hydrolyses – Atypical "

Adverse drug effect of Sch:

- Hyperkalemia ((Burns), nerve injury, crush injury
- Malignant hyperthermia
- ↑ Intra ocular/gastric pressure

→ those who are having genetic abnormality in Ryanadine receptor.

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Primaquine – Causes hemolysis only in G6PD deficiency.

Pharmacogenomic / Idiosyncracy – Ryenodine Receptor
↓
Occurs disease in only genetic abn person.

T/t => Daulrolene
(Directly acting SMR)
↓
DOC for : Malignant hypothermia
Neuroleptic malignant Syndrome.

SMR – causes pain on injection – Rocuronicum.
GA causing pain " – Propofol
Post. op muscle pain – Sch
Analgesic used during Sx causing Post-op truncal rigidity – Fentanyl, Alfentanil
T/t – Wooden chest Syndrome.

Antibiotics causing SMR :
- Aminoglycosides (Max^{m}) – Neomycin
- Macrolides
- Quinolone
- Tetracyclines

Aminoglycosides – Inhibit Release of Ach
Similar to Botulism toxin.
T/t – Neostigmine + Calcium.

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N_N :

Location: Autonomic ganglia (Most)
Adrenal medulla
CNS

Autonomic ganglia –

Sympathetic:

Preganglionic (< Ach N_N) Post-ganglionic NE

Ganglia

Parasympathetic:

Preganglionic (< Ach N_N) Post-ganglionic Ach.

Ganglionic Blockers (N_N)
- Hexamethonium
- Trimethaphan
- Mecamylamine → (Smoking control)

useful to produce controlled hypotension.

Anti-smoking drugs:

First line drug (therapy)
- Varenicline ($\alpha_4\beta_2$ nicotinic agonist) – Suicidal thoughts
- Nicotine (patch, inhaler, lozenges, chewing gum)
- Bupropion – NDRI (Norepinephrine Dopamine Reuptake Inhibitor)
  Antidepressant
  Weight loss
  ADHD (off label)
  Adverse drug reaction – Seizure.

Second line therapy:
Clonidine (α_2 agonist)
Nortriptyline (TCA)

ADR = Adverse Drug Reaction

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Miscellaneous:

Rimonabant

Topiramate – Antiepileptic

ADR – Weight loss, Nephrolithiasis.

Mecamylamine

Rimonabant: Inverse agonist/ Antagonist of Cannabinoid 1 receptor.

- Weight loss
- Prevents craving of alcohol.

ADR – Psychiatry problems (withdraw)

ADHD (Attention deficit hyperactivity disorder):

Drug used – Amphetamine

↓

Causes – Cardiotoxic
Addiction
Appetite Suppressant.
(Failure of growth)

First line drugs:

- Methyl phenydate (First choice)
- Atomoxetine

↓

Ritalinic acid (Metabolite).

Other drugs:

~~Pl~~. Pemoline (Hepatotoxic)

Modafinil – Use: Narcolepsy
Shift worker
Obstructive sleep apnea.
ADHD. (FDA – Unapproved)

Newer drug under Narcolepsy:
H_3 inverse agonist
↓
Pitolisant (OR) Tiprolisant
Narcolepsy (Orphan drug status)

Drug useful for t/t of obesity:
- Sibutramine (β_3 agonist) – Cardiotoxic (Withdrawn)
- Orlistat (lipase inhibitor) – Steatorhoea
- Olestra (Sucrose polyester) – cooking medium.
- Rimonabant (Canabinoid 1 antagonist) – Withdrawn
- Leptin (Endogenous slimming peptide)

Combination therapy:
Bupropion + Naltrexone (opoid antagonist)

Bupropion + Zonisamide (Antiepileptic)

Phentaramine + Topiramate (Antiepileptic)
(Sympathetic stimulant
Causing
Apetite suppressant)

Newer drug: 5HT2c agonist – LORCASERIN
S/E – Serotonin Syndrome.

GLP-1 → LIRAGLUTIDE
FDA approved drug for obesity.

Extra point: Antiepileptic causing Wt. loss
- Topiramate
- Zonisamide
- Felbamate

Antiepileptic causing Wt. gain:
- Sodium Valporate
- Gabapentin

Felbamate < Hepatic failure (F/E)
Aplastic Anemia.

Type 2 DM c obesity — 1st line drug — Metformin
Non-diabetic c obesity — No Metformin.

Antidiabetic causing:
Weight gain :— Insulin, Insulin secretagogues.
- Sulfonyl ureas, meglitinides, Thiozolindindiones.

Weight loss — Pramlintide, GLP-1 agonist, SGLT-2 inhibitor

Weight neutral — Metformin, DPP4 inhibitors.

OPC's = Organophosphorus compd.

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ANTI CHOLINESTERASE

Reversible

Carbamates
→ Physostigmine
(Natural origin)
Alkaloid (plant)
• Highly lipid soluble
DOC : Atropine poisoning
(Belladona)

→ Neostigmine
Pyridostigmine
Edrophonium
(Water soluble)
No CNS effect.

Neo – direct action on NM receptor
Pyri – long acting
Orally active
Edro – Anionic site binding
• Rapid dissociation
• Used for Δ of myasthenia gravis.
(Tensilon test
or, Ameliorative test)
– Provocative test
(done by injecting d-Tubocurarine)

Acridine
→ Tacrine
↓
Hepatotoxic
So, not used in Alzheimer's

Irreversible

OPC's
→ Dyflos
→ Echothiophate
→ Parathion
→ Malathion
→ Diazinon
(Insecticide)
→ Tabun
→ Sarin
→ Soman
(Nerve gas or, war gas.)

Malathion – Pediculosis (lice) infestations
Echothiophate – Use in Glaucoma
S/E Cataract

Ageing of enzyme
Tabun (Slow)
Sarin (3-5 hrs)
Soman (2min) – Fastest acting

t/t – Atropine + Pralidoxime
In convulsion – Diazepam

Carbamate
→ Carbaryl
→ Propoxur
(Baygon)

Rivastigmine, Donepezil, Galantamine } useful for t/t of Alzheimer's ds
↓
deficiency of Ach.

OPC's poisoning:

Parathion, Malathion, Diazinon
Cholinesterase inhibitors
(Irreversible)

1st line DOC : Atropine (Muscaranic Blocker)
↓
Dose is depends upon Sign & Symptoms of Atropinisation:
- HR > 100/min
- Pupil Size
- Pulmonary Secretion
- Secretion

Max^m upto — 200 mg.

Oximes:
- Cholin Esterase ~~inhi~~ reactivation.
- Only used for t/t OPC's poisoning
not carbamate poisoning.

eg: • Pralidoxime (1-2g, slow i.v., 15-30 min)
• Obidoxime (more potent)
• Diacetyl mono oxime (Highly lipid Soluble)
↳ More CNS action

S/E — HTN
↳ T/t — Phentolamine (Non-selective α Blocker)

Myasthenia Gravis (MG):

Ameliorative test
Provocative test

Definitive test → Anti Ach Receptor Radioimmuno Assay.

Confirmatory → Single fibre Electro Myography. (SF-EMG)

First line drug — Neostigmine
Pyridostigmine

Others — Corticosteroids
Thymectomy
Plasmapheresis
IvIg.
} To remove autoantibody.

Other immunosuppressant — Azathioprine
Cyclosporine.

Monoclonal antibody — Rituximab
↓
Target CD20.

Remission / Exacerbation:

Rapid Recovery — Plasmapheresis
IvIg.

Quinine
- C/I in MG
- It is SMR
- Used in Nocturnal leg Cramps.

- Avoid Aminoglycoside in MG.

MEMANTINE – NMDA Blocker
useful for moderate to severe Alzheimer's ds.

Drug useful in cervical ripening – VALATHAMATE
↓
Anticholinergic drug
Smooth muscle relaxant.

Diphenoxylate – Opioid
Anti diarrhoeal
Addiction
↳ Atropine ↓ addiction of Diphenoxylate

Glycopyrolate – Anticholinergic
Preanesthetic
Qualernary compd.

Scopolamine – Also K/A Hyoscine → CNS depressant (Sedation)
Used in motion sickness.
DOC : Hyosine → Narco Analysis

1st Gen. (H1 + M) : Promethazine
↓ In treating Allergic condn
↓ In Motion Sickness
↓ treating EPS (Extra pyramidal Symptom

For Sea Sickness – Same t/t.
↳ Meclizine – 1st gen. long acting Anti-histamine.

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For Mountain sickness : Acetazolamide
(Carbonic Anhydrase Inhibitor)

Morning sickness : Doxylamine c Vit B6
↓
antiemetic Vitamin

Vit B6 (In Pyridoxine) :
- Anti-emetic
- Controls intrauterine Seizure.

Stimulant of dopa decarboxylase
C/I - Levodopa

Vit B6 should not be given c Levodopa.

Vit B6 definitely given c Anti TB drug (Isoniazid)
↓
To correct peripheral neuropathy.

Antidote for Vit B6 - 4 deoxy pyridoxine

Folic acid -
Prophylactic - 400 µg daily in pregnancy.
Previous H/o Neural tube defect - 5 mg/day.

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Drug having Anticholinergic activity:

- TCA's
  - Amitriptyline
  - Imipramine — Nocturnal enuresis
    DOC: Desmopressin

- Anti Psycholics
  - Thioridazone
  - Clozapine

- SMR
  - Pancuronium
  - Gallamine

- Class Ia Anti arrythmic drugs.
  - Quinidine
  - Procainamide
  - Disopyramide (Highest anticholinergic property).

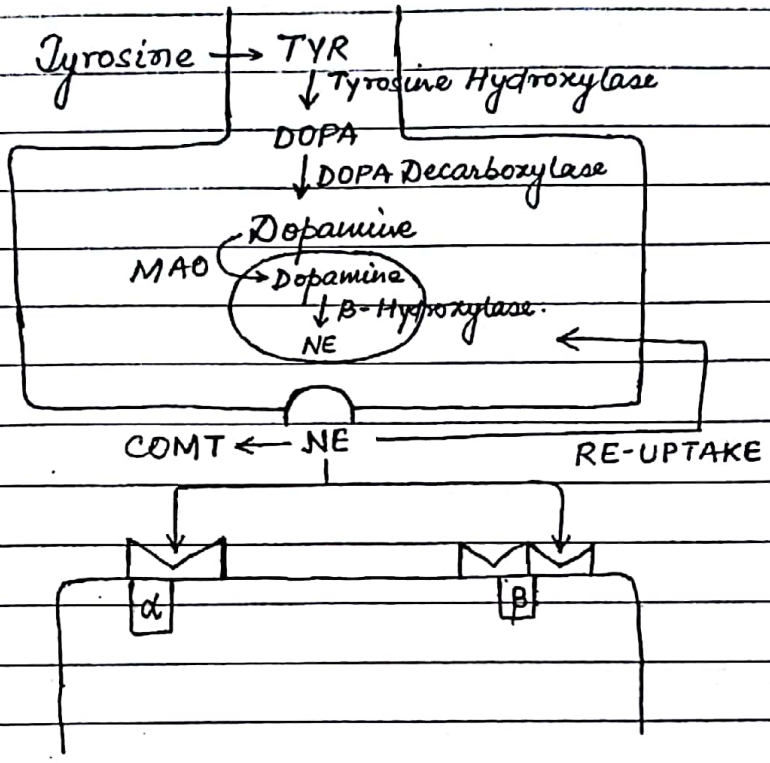
- 1st H_1 Blocker
  - Promethazine

- Amantidine

Meperidine (Pethidine)
↳ opoid analgesics
↳ C/I in MI pain
↓
Morphine is Used.

ADRENERGIC DRUGS

Synthesis, storage, Release, Metabolism of NE :



Synthesis of NE → Only in the vesicle.

Catecholamine — Dopamine
NE
Epinephrine

Monoamines — Dopamine
NE
Seratonin.

For metabolism of NE — MAO
COMT

- Even though NE undergoes metabolism by MAO & COMT, enzymatic degradation is not involved in termination.

- NE action is terminated by Re-uptake.

- Rate limiting enzyme of Synthesis of NE – Tyrosine Hydroxylase.

- Drug inhibiting Tyrosine hydroxylase – Alpha methyl para thyrosine (METYROSENE)

- Dopa decarboxylase inhibitor – Carbidopa Benseraside.

- Reserpine → Anti HTN agent
  → Vasicular uptake inhibitor.
  - S/E → Sucidal depression.

- β-hydroxylase blocker – Disulfiram (Used in alcoholism deaddiction)

Ethyl alcohol
↓ Alcohol dehydrogenase
Acetaldehyde
↓ Acetaldehyde dehydrogenase ⊖ Disulfiram.
Acetic Acid

New drug – DROXIDOPA
(Prodrug of NE)
- Used in Neurogenic Orthostatic hypotension
- Hemodialysis induced hypotension.

BRETYLIUM : Class III drug
K^+ - Channel blocker.
Also called Chemical defibrilator.

Release of NE is blocked by – Bretylium
Guanathidine.

NE Re-uptake inhibitor – SNRI, NDRI, TCA, Cocaine.

Cocaine → One & only local anesthetic causing HTN.
- Causes mydriasis by acting on α_1 on the radial muscle.

Adrenergic Receptor: < α / β
↓
(Henry Ahlquist)

α - Receptor: < α_1 → post-synaptically (location).
α_2 → pre-synaptically
→ Inhibition of release of NE.
→ auto receptor for NE

α_2 agonist:
eg: Clonidine, Methyldopa, Guanafacine > Centrally acting Anti HTN

Guanabenz
Moxonidine
Rilmonidine
Apraclonidine
Brimonidine
} Useful in Glaucoma.
MOA - decreases Aqueous Secretion

S/E - Drowziness → Not safe in children.

Tizanidine → Centrally acting SMR.

Dexmedetomidine. → Used as Sedation (ICU pts) & Pre-anesthetic medication.

Methyldopa : DOC for t/t of HTN during pregnancy.

Hypertensive Emergency :
Labetalol (β+α blocker)
Hydralazine (K⁺ channel Opener)
↳ Arteriolar dilator.

Eclampsia - $MgSO_4$.

Methyldopa may cause hemolytic anemia to mother
↓
Coomb's test +ve

Drug avoided in pregnancy : ACEi (Renal & pulm agenesis)
ARB's
Sodium nitroprusside (contain Cyanide)

Apraclonidine : Specific S/E - lid lag.
Brimonidine : S/E - Anterior uveitis.

α_2 antagonists: ↑ NE release.

Yohimbine – Used in Hypotension & Sexual stimulation

Idazoxan

α_1:

Location – Post synaptically.

① α_1 seen on vascular smooth muscle.

Action → Vasoconstriction

α_1 agonists:

Based on vascular action

Useful in t/t of Hypotension

Nasal congestion.

Selective α_1 agonists for t/t for Hypotension:

Methoxamine

Mephentermine

Midodrine.

Selective α_1 agonist for t/t for Nasal congestion:

Cause Atrophic Rhinitis (Rhinitis medicamentosa) – Naphazoline, Oxymetazoline, Xylometazoline.

α_1 Receptor – Radial muscle of iris → Mydriasis

↳ Phenylephrine

α_1 Receptor seen in internal urethral sphincter

↳ Causes sphincter constriction

↳ Retention of urine.

α_1 blocker used in BPH

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Vesico ureteric junction α_1 Receptor +nt.

α_1 blocker useful in t/t of – lower ureteric calculi

α_1 seen on Vas deferens of penis.
Action → Ejaculation.

S/E of α_1 Blocker – Impairment of Ejaculation.

Directly acting Sympathomimetic
α, β agonists
Adrenaline, NA.

Indirectly acting sympathomimetic:
Tyramine → Act on vesicle → Causes release of NE.
↓
Causes depletion of storage of NE
↓
Tachyphylaxis → Rapid tolerance

MAO inhibitors taking c Tyramine containing food (cheese, wine, bread) causes HTN, it is called Cheese reacn.
↓
DOC for t/t of HTN due to cheese reacn: Phentolamine
(non-selective α blocker)

Mixed action Sympathomimetic – EPHEDRINE
↓
causing hypotension
↓
Spinal anesthesia.
Safe in pregnancy.

Selective α_1 Blocker:

eg: Prazosin (PDE inhibition property).
Doxazosin > Apoptotic action on Prostate.
Terazosin

α_1A blocker → mainly acting on bladder.
- Silodosin
- Alfulosin
- Tamsulosin

Indoramine, Urapidil. > useful in Hypertensive Emergency.

PRAZOSIN:

- Vasodilation → on smooth muscle.

Use – HTN
PVD
CCF
Scorpion Bite.

S/E – Postural hypotension
(1st dose hypotension)
- Impairment of ejaculation.

Selection of Prazosin as Anti-HTN:

① HTN c dyslipidemia
② HTN c elderly male c BPH.
③ Can be used in diabetics c HTN.

HTN c dyslipidemia:

Choice – Prazosin
Anti HTN avoided – Non-selective β-blocker
Thiazide ~~use~~ diuretics

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No problem c → CCB, ACEi, ARB, clonidine.

HTN c diabetes :
Choice → ACEi = ARB > CCB
Unfavourable (avoid) → β-blocker
Diuretics.

Anti-HTN causing Erectile dysfunction —
Highest risk — Diuretics (Thiazides)
High risk — β-blocker (Atenolol, Carvedilol,

In BPH → Static obstruction is overcome by
Finesteride + Tamsulosine.
↓ (Rapid Benefit)
It takes 3-6 months for action.
Tamsulosine overcomes dynamic obstruction.

Pt. on Tamsulosine may cause risk of floppy iris syndrome → going for cataract.

Non-selective α-blocker:

Irreversible – Phenoxybenzamine

Reversible – Tolazoline, Phentolamine.

PHENOXYBENZAMINE:

Definitive therapy for t/t of HTN in Pheochromocytoma – Phenoxybenzamine.

For controlling intra-operative HTN during pheochromocytoma Sx – i.v. Phentolamine
i.v. Nitroprusside.

Don't use Propanolol as a 1st line drug for t/t HTN due to Pheochromocytoma.

In Phechromocytoma Sx – ~~Drug~~ Halothane is C/I
↓
sensitize the myocardium for catecholamine
↓
Causes MI.

Phentolamine:

Use – DOC → for t/t of Clonidine withdrawl HTN
DOC for t/t of HTN due to cheeze reacn.
In intra-op HTN during Pheochromocytoma Sx
Oxine induced HTN.
Useful for t/t of Erectile dysfunction (injectable drug)

PIPE Therapy (Pharmacologically induced penile erection):
Injectable drugs used for t/t of erectile dysfunc^{n}:
- Alprostadil (PGE1 analogue)
- Phentolamine
- Papaverine (Non-selecting PDE inhibitor).

β-Receptors → G-protein couple acting via Gs pathway.

β_1 β_2 β_3

β_1 →
Location – Myocardium
Kidney.

Action (Heart) → ↑ HR
↑ Force of contraction
↑ C.O.
In kidney → Renin release.

Selective β_1 agonist:
Dobutamine (Synthetic Catecholamine)

eg. of synthetic Catecholamine
① Isoprenaline → acting on β_1 β_2 β_3
② Dopexamine → D_1, β_2
③ Dobutamine → β_1 ($t_{1/2}$ = 2 min)
④ Fenoldopam → D_1

Dobutamine Used in → Stress ECHO
D_1 receptor seen in Renal blood vessel → Renal Vasodilation

∴ Fenoldopam Used in → • iv infusion
• HTN emergency c Renal impairement.

β_2:
Location: Smooth muscle < Vascular
Visceral.

Stimulation of β_2 → Vasodilation.

Visceral —
Bronchial muscle → Bronchodilation.

β_2 agonist useful for t/t of Bronchial Asthma:
Salbutamol, Terbutaline } short acting
Useful for Acute asthma.
Salmeterol, Formeterol, Indacaterol } long acting
Useful for Chronic asthma

Salbutamol:
M/C S/E — Tremors
Palpitation.

Uterus → Action → Uterine muscle relaxation.
Tocolytics — Ritodrine (FDA approved)
Isoxuprine

β_2 agonist having anabolic action — Clenbuterol.

Phospholypase-Gq ← α_1] – G-Protein Couple receptor.
Adenyl cyclase – Gi ← α_2

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β_2 – Role on metabolism

Carbohydrate	Potassium	Lipid
– Hyperglycemia	– Hypokalemia	– Reducing blood cholesterol.

Hyperkalemia:
Mild → 5.5 to 6.5 m Eq/L
Moderate → 6.5 to 8.0 meq/L
Severe → > 8.0 m Eq/L

For Rapid control of potassium in Hyperkalemia (emergency) – Insulin + Glucose infusion.

For Hyperkalamia + ECG abnormalities
– Calcium Gluconate.

β_3:
Location: Adipose tissue

Selective β_3 agonist – SIBUTRAMINE
– lipolysis
– withdraw due to Cardiotoxic.

MIRABEGRON:
– β_3 agonist
– Relax detrusor
Used in – Overactive bladder.

Q Which one of the following don't have significant ~~dopamine~~ dopaminergic activity –
A) Dopamine (D_1, β_1, α_1) C) Fenoldopam (D_1)
B) Dobutamine (β_1) D) Dopexamine (D_1, β_2)

Dopamine : has D_1, β_1, α_1 action.

↓ ↓ ↓

< 2μg/kg 2-5 5-10 μg/kg.

DOC for Cardiogenic Shock — Dopamine.

Shock	T/t
Cardiogenic	NE or Dopamine
Cardiogenic c̄ oliguria	Dopamine.
Anaphylyclic	Adrenaline
Secondary	α-blocker
Adrenal insufficiency	Steroids

Blood pressure :

BP = CO X Peripheral resistance.

↓ ↓

SBP DBP

Effect of Isoprenaline on BP :

- β_1 ; β_2, β_3 action.
- No α action.
- ↑ SBP ; ↓ DBP → Reflex Tachycardia
- Wide pulse pressure.

NA : α_1, α_2, β_1

No β_2 action

↑ SBP ; ↑ DBP → Reflex bradycardia

Adrenaline on BP : acting on α_1 α_2 β_1 β_2

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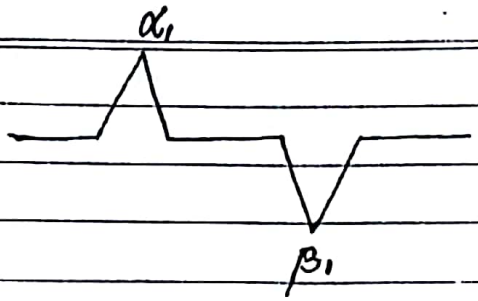
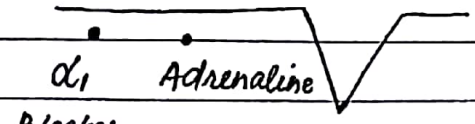


Biphasic response of Adrenaline on BP.
- Adrenaline cause initial ↑ BP & later ↓ BP.

Dale's vasomotor reversal phenomenon:



If we give α_1 blocker before adrenaline, adrenaline act only on β_2 causing fall in BP.

Q. All are lipid insoluble β-blocker except?
A) Nadalol
B) Propanolol
C) Atenolol
D) Sotalol

Lipid soluble β-blocker – Propanolol (Highly soluble)
↓
- M/commonest drug used for prophylaxis of migraine.

DOC –
- Performance anxiety
- Essential tremor
- Akathesia

Lipid insoluble β-blocker – Nadalol (Most longest acting >40hr)
Atenolol
Sotalol
↓
Long duration of action
No hepatic metabolism
Unsafe in Renal failure – Dose adjustment required.

β-blocker

Non-selective β-blocker: 1st generation β-blocker
- Drug block both β_1 & β_2.

Cardioselective β-blocker: 2nd generation β-blocker
(Predominantly blocks β_1 blocker)

- No selective β_2 blocker.

#. 3rd generation β-blocker – β-blockers c additional properties.

Cardioselective β-blocker:
Nebivolol (Most Cardioselective; Releases NO) → Vasodilation
Betaxol - Useful in Glaucoma; Safe in asthmatic.
Bisoprolol - Useful in CCF
Atenolol
Esmolol - Most ultra short acting (~9 min), i.v., Emergency.
Acebutolol
Metoprolol - Useful in HTN, Angina, MI, CCF.
Celiprolol

3rd generation β-blocker:
① β-blocker having α blocking property –
Labetalol - β & α blocker
- Use → HTN emergency in pregnancy.
- S/E → Postural hypotension, hepatotoxic.

~~Carbi~~
Carvedilol - β & α blocker
- Antioxidant
- USE → in CCF. → Bisoprolol
Metoprolol.

② β-blocker having NO releasing property –
Nebivolol
Nipradilol

③ β-blocker having K^+ channel opening action –
Tilisolol

④ β-blocker having K^+ channel blocking property –
Sotalol – Class III antiarrhythmic group.

BUTOXAMINE :
- Only selective β_2 blocker
- Used for research purpose, not for therapeutic purpose.

β-blocker having highest membr stabilizing
↓
Na^+ channel blocking property
or local anesthetic action.
→ Propranolol.

β-blocker having highest intrinsic sympathomimetic
→ Pindalol

β blocker having favourable effect on lipid profile
→ Pindolol.

Antidote for β blocker poisoning – Glucagon.

Uses of β-blockers:

① CNS – Performance, Anxiety
Prophylaxis – Migraine
Akasthesia
Essential tremors.

② Eye – Glaucoma
↳ β blocker – Timolol
Betaxolol
Carteolol
Levobunolol
Metipranolol
} ↓ aqueous secretion

Systemic S/E of Timolol – Bradycardia
Heart block
Bronchospasm

Betaxolol – Safe in asthma.

Local S/E of Timolol – Blepharo conjunctivitis
Nasolacrimal duct obstruction

③ Thyroid – Hyperthyroidism
↓
- propranolol inhibits peripheral conversion of $T_4 \rightarrow T_3$
- Symptom relief.

④ CVS – HTN Arrhythmia Dissection of aorta
Angina CCF TOF
MI HOCM

A/c Joint National committe guidelines

First line drugs used in t/t of HTN:

- Thiazides
- ACEi
- ARB
- CCB

↳ No β blockers.

(5) Useful for Portal hypertension (Prophylaxis)

↓

Propranalol

DOC for t/t of bleeding due to esophageal varices

- OCTREOTIDE

↓

most potent vasoconstrictor

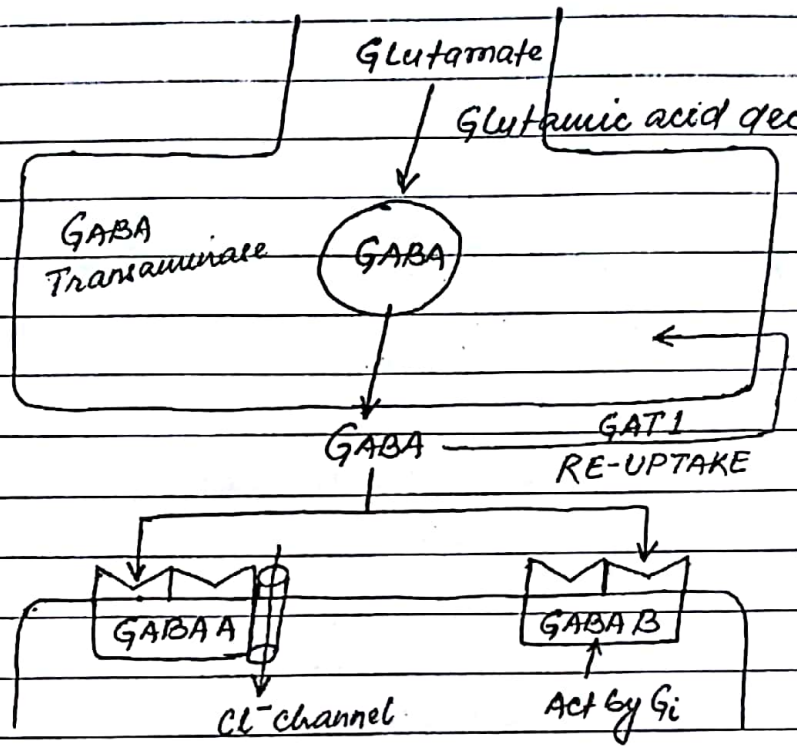
- controls bleeding

- Terlipressin – V_1 agonist can be added.

DOC for prophylaxis – Propranolol, Nadalol.

Central acting drugs

GABA :



Metabolism by — GABA transaminase.

Action of GABA : When GABA enters GABA A, Cl^- channel enters causing hyperpolarization.

Drugs acting via GABA A pathway

Benzodiazepine Barbiturates.

BZD binding to BZD receptor which is made up of α, γ unit of GABA A.

BZD = GABA facilitatory.

↑ frequency of Cl^- channel opening.

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MOA of Barbiturates –
– Barbiturates binding ē α, β units of GABA A.

Barbiturate : Low dose → GABA facilatatory
High dose → GABA mimetic.
↑ duration of Cl^- channel opening.

Benzodiazepine (BZD):
Action (USE) → Sedation
Anti-convulsion
Anti-anxiety
SMR.

Diazepam – DOC for Acute febrile seizure (Rectal Diazepam)
Status Epilepsy (currently DOC – i.v Lorazepam)
Delirium tremors.
Lorazepam – DOC for Status epilepsy.
Alcohol withdrawl : DOC : Chlordiazepoxide.
(Delirium tremors)

Midazolam, Remimazolam > short acting
↳ Ultra short acting.
→ Anaesthetic property.

Alprazolam – used in Insomnia, Anxiety disorder

Long term use of BZD – Addiction
Tolerance
Day time sleeping.

BZD safe in liver failure pt:
- Temazepam
- Oxazepam (Metabolite of Diazepam).
- Lorazepam.

Sleep onset Insomnia:
Z compounds — Zolpidem (Most common)
Zopiclone
Zaleplon (Shortest)
All are short acting

FLUNITRAZEPAM: Date Rape drug.
Causes Anterograde amnesia.

KETAMINE: Also date rape drug.

BZD poisoning —

Antagonist:
Competitive antagonist — FLUMAZENIL
↓
prevent binding of BZD ē
α, γ unit of GABA A.
- Specific antidote of BZD.
- Given i.v.
- $t_{1/2}$ = 60 min

BICUCULLINE — Competitive antagonist of GABA
Non competitive inhibitor of BZD.

PICROTOXIN — Direct Cl^--channel blocker.

Inverse agonist of BZD Receptor — β-Carbolin

Flumazenil used for — BZD poisoning
β-carbolin poisoning
Z-compound poisoning.

BARBITURATES :

Long acting	Short acting	Ultrashort acting
- Primidone	- Secobarbitone	- Theopentone Sodium
- Phenobarbitone	- Pentobarbitone	- Methohexitone.

Theopentone sodium — Indication
- iv induction GA
- Re distribution
- Cerebro protective

Other uses — Narco analysis
Status epilepsy.

Methohexitone — causing convulsion.
Used in Electro convulsive therapy.

Phenobarbitone — metabolite of Primidone.
↳ Useful in Anticonvulsion in pregnancy & pediatrics.
↳ In children it causes hyperkinesia.

General properties of Barbiturates:

- Algesic property (produce pain)
- Narrow therapeutic index. (Hence – unsafe)

↓ only

∴ Used in – Epilepsy
Anaesthesia

Clinical manifestation of Barbiturates :-

- Flabby muscle
- Comatose
- Shallow & falling Respr
- Bullous eruption.

T/t:

- No specific antidote.

- Poisoning → Forced alkaline diuresis
Hemodialysis.

All barbiturates are microsomal enzyme inducer.

Since powerful enzyme inducer
∴ C/I – acute intermittant porphyria.

GABA analogues.

GABA Reuptake inhibitor: TIAGABINE

GABA Transaminase inhibitor: VIGABATRINE
SODIUM VALPROATE

Glutamic acid decarboxylase activator: VALPROATE

VIGABATRINE – DOC for infantile Spasms (Tuberous Sclerosis)

SE → Visual field defect
SE → Psychosis

For Simple Infantile Spasm – ACTH

LEVATIRACETAM: ligand for SV2A protein
↓
Synaptic Vesicle
– modify synaptic release of Glutamate/GABA.
↓
Controls Seizure

New drug – GABAPENTIN, PREGABALIN] Useful in DM neuropathy pain, Post herpetic neuralgia.

GANAXALONE
– Neurosteroid
– Direct Cl^- channel opener
Useful in – Absence seizure
Catamenial seizure.

GABA B (G-protein Coupled Receptor)
↳ Agonist – BECLOFEN
Antagonist – SACLOFEN

BACLOFEN – Centrally acting SMR
Useful in – Hiccough
Craving of alcohol.

MELATONIN:
Sleep inducing hormone
Secreted from pineal gland.

Melatonin analogue – REMELTEON
↓
MT1 MT2
↓
Useful in sleep onset insomnia
No risk of ABUSE/ TOLERANCE.

TASIMELTEON – Useful in t/t sleep awake disorder in blind.
↓
Melatonin analogue.

AGOMELATINE – Agonist on MT1/MT2
Antagonist on 5-HT 2C
Melatonin analogue ∴ antidepressive property.

SUVOREXANT → FDA approved drug for insomnia.
ALMOREXANT → Non-selective OREXIN receptor antagonist.
↓
another orexin receptor antagonist.

Glutamate

AMPA receptor → open Na^+, Ca^{2+} channel

NMDA receptor → Opens Na^+, Ca^{2+} Channel

Both are ligand gated receptor.

T/t of epilepsy – Glutamate antagonist

AMPA blocker	NMDA blocker
Topiramate	Felbamate
Lamotrigine	Valproate
Remacemide	
Perampanel	
Talampenal	

Actions of Sodium Valproate:

- GABA agonism
- Anti glutamate
- Na^+ channel blocking action
- Ca^{2+} Channel blocking action
- Broad spectrum anti-epileptic.

Lennox Gestaut Syndrome:

℞ → FELBAMATE – S/E – Hepatic failure
Aplastic anemia.

Currently Used:
- VALPROATE
- BZD
- RUFINAMIDE (Na^+ channel blocker)

TOPIRAMATE :

Use → Epilepsy
Prophylaxis of Migraine
Alcohol (Anti craving)
Smoking (")

S/E → Renal Stone
Wt. loss

LAMOTRIGINE :

Useful in – Epilepsy
BPD depressive

Rarely cause SJS (Steven Johnson Syndrome).
TEN (Toxic epidermal necrolysis)

NMDA blockers :

Anaesthetic action:
- Ketamine : – Dissociative anesthesia
- Xenon
- N_2O (Laughing gas) → S/E – Megaloblastic Anemia.

Memantine → Useful in Alzheimers
Acamprosate → GABA agonist property, Craving alcohol.
Amantidine → Useful in Parkinsonism
Methadone → DOC for Opioid deaddiction.
Riluzole → Useful for ALS
Phencyclidine → Angel dust.

Dopamine as a Neurotransmitter :

Dopaminergic pathway :

① Meso-limbic fibre – extend upto prefrontal lobe secrete dopamine.
↑ dopamine – cause Psychosis

② Nigro-striatal neuron – (N) func^{n} is to synthesise & release dopamine in corpus striatum.
- helps in initiation of movement.

In corpus striatum – amount of Ach & Dopamine balanced.
As ↑ age – adequate amount of dopamine is not secreted & there is ↑ in Ach activity.
Muscle rigidity occurs due to ↑ Ach.
- Hypokinesia, Tremor, ~~Rigidity~~ Rigidity.

③ Tubero infundibular fibre – extend from hypothalamus to anterior pituitary.
- Dopamine analogue are used for ↓t of galactorrhoea.
- Dopamine act on D_2 receptor in the brain & causes psychosis.
- Any drug blocking D_2 & causing anti psychotic effect is called ATYPICAL ANTIPSYCHOTIC.

Two most common S/E of antipsychotic (EPS
Galactorrhea.

Levodopa & Carbidopa : long term S/E

↓

① Psychosis

② Choreoathetoid movement (Dyskinesia).

PSYCHOSIS:

- Overaction of Dopamine.
- D_2 blockers → Conventional / Typical Antipsychotic.

Conventional / Typical Antipsycholic drugs

Phenothiazine	Butyrophenones	Thioxanthenes.
Chlorpromazine	Haloperidol	Thiothixene
Trifluperazine	Trifluperidol	Flupenthixol.
Thioridazone	Droperidol	
Fluphenazine	Penfluridol-LA	

Typical antipsycholic = Neuroleptic agents.

Most potent D_2 blocker / Antipsycholic = Butyrophenone

↓

Max^{m} EPS produced

THIORIDAZINE — S/E → Corneal pigmentation
Cataract
Retinal degeneration.

Most potent Antipsycholic — HALOPERIDOL
↓
Cause Maxm EPS
Less ANS side effect.

CHLORPROMAZINE — causes Cholestalic jaundice.

Drug induced Parkinsonism:
TOC — Centrally acting Anticholinergic
↓
Trihexyphenidyl (BENZHEXOL)

Other — Benztropine
Biperiden
Procyclidine.

PROMETHAZINE — 1st gen. antihistamine
have anticholinergic action
So, used in EPS.

Extra pyramidal Syndrome:
① Drug induced Parkinsonism
② Acute muscular dystonia: PROMETHAZINE
BENZHAXAL
③ Tardive dyskinesia: No specific t/t
Symptomatic — Valproate, Vit. E.

VALBENAZINE (Newer drug)
- Acts by Vesicular monoamine transporter 2 inhibitor.

④ AKATHESIA — DOC : Propranolol

⑤ Malignant Neuroleptic Syndrome : DANTROLENE
↓
directly acting SMR.

Anti-Parkinson drug:

LEVODOPA :

↳ Protein meals reduces absorption of levodopa.
Vit-B_6 (Pyridoxine) should n't be given c levodopa bcoz it stimulate peripheral conversion.

Peripheral toxicity:

M/C S/E of levodopa — Nausea & Vomitting
Alteration in taste sensation.
↓
due to stimulation of D_2 receptor in CTZ.

D_2 receptor blocker — Domperidone
Metaclopramide.

Only domperidone is useful in t/t of vomitting due to levodopa.
Metaclopramide is not used ~~by~~ bcoz it crosses BBB & reduces efficiency of levodopa.

Causes — Cardiac arrhythmias
Excerbation of angina
— due to D_1, β_1, α_1 activation.

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LEVODOPA + CARBIDOPA
↳ Dopa decarboxylase inhibitor

Long term S/E → Abnormal choreo athetoid movement
→ Psychosis

Huntington's Chorea, Tourette Syndrome] movement disorder due to overaction of dopamine.

↓

T/t – DOC : TETRABENAZINE
(Dopamine Depletor
other – Chlorpromazine
Haloperidol.

Levodopa is Precursor of melanin
– C/I in melanoma

Chronic therapy of levodopa may cause On & off pheromenon
↓ ↓
dyskinesia Severe parkinsonism
↓
Rescue therapy
– APOMORPHINE (D_4)
given S/C.

Abrupt withdrawl of levodopa → Neuroleptic malignant Syndrome.

AMANTIDINE:

Influenza

Influenza A	Influenza A & B (Bird flu)
- Amantadine	- Oseltamivir
- Rimantadine	- Zanamivir.

Oseltamivir — 75 mg / 1 BID / 5 days — Oral
↳ Prodrug — Causes Nausea & Vomitting.

Zanamivir — Intranasally — Bronchospasm

Vaccination:
PERAMIVIR (Neuraminidase Inhibitor)
↳ IV (Intravenous)

Amantidine:
- Anti cholinergic
- Dopaminergic agonist
- NMDA antagonism.

- Useful in Parkinsonism

S/E — Ankle edema
Livido reticularis. (Net like skin rashes).

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Ergot D_2 agonist : Bromocriptine
Pergolide
Cabergoline

Common S/E of these 3 drugs — Erythromelalgia.
Cardiac valve fibrosis.

Pergolide — Causes max^{m} Cardiac valve fibrosis.

Other uses of Bromocriptine :
- Prolactinoma.
- Acromegaly
- Type 2 DM

Non- Ergot D_2 agonist : Pramipexole] M/C S/E Psychosis.
Ropinirole]
Rotigotine (Transdermal)
Advantage : No peripheral vasoconstriction.

[Pramipexole / Ropinirole] — S/E → Compulsive shopping
Kleptomania
Sexual desire
→ Useful for t/t of Restless leg Syndrome.

COMT inhibitors

JALCAPONE

Dangerous toxicity
- Rabdomyolysis
- Severe Diarrhoea
- Hepatotoxicity.

Urine – Yellowish Orange.

ENTACAPONE
- doesn't crosses BBB.

SEROTONIN (5-HT)

Source – Tryptophan

Func^n of 5HT1A – Inhibition of release of Serotonin.
↓
Autoreceptor of Serotonin.

Monoamine undergoes metabolism by Monoamine oxidase (MAO). They produce metabolite 5-hydroxyindole acetic acid.

In Carcinoid tumour – ↑ 5-hydroxy indole acetic acid.

Serotonin undergoes reuptake causing ↓ central serotonin.

Action of Serotonin on 5HT1 B/D – Vasoconstriction
↳ SUMATRIPTAN (Use - Migraine)
(mainly 1D ; min^m 1B)

Action of Serotonin on 5HT2 – Shizophrenia
(5HT2A/2C)
↳ Clozapine
Risperidone
Olanzapine

Action of Serotonin on 5HT3 :- Nausea & Vomitting

5HT3 antagonist – Ondaselron
Granisetron

Action of serotonin on 5HT4 : Diarrhoea.

Selective 5HT4 agonist – Cisapride | withdrawn bcoz of QT prolongation on ECG.
Mosapride
Tegaserod

All serotonin receptors are G-protein coupled receptor. except 5HT3 (ligand gated receptor)

Acute Migraine:
Main issue – Vasodilation
For t/t of Acute migraine – Vasoconstrictor
↓
Ergot Alkaloids – Ergotamine
5HT1 B/D agonist – Sumatriptan (DOC)
Rizatriptan
Almotriptan
Frovatriptan
Zolmitriptan

Care is taken for HTN & IHD in these pts.

St. Anthony's fire → chronic treatment c ergot alkaloid cause peripheral vasoconstriction (gangrene of foot)
Poisoning – Ergotism

BUTOPHANOL – Opoid
Used intranasally for Headache.

Drug useful for Prophylaxis of chronic Migraine:
① M/c drug – Propranolol (β-blocker)
② CCB – Flunarazine
(Na⁺ channel blocking & Antioxidant property)
③ Anti-convulsant – Valproate
Gabapentin
Topiramate
④ TCA – Amitryptaline.
⑤ Clonidine
Onabotulinum toxin A
⑥ $5HT_2$ blocker
- Pizotifen
- Cyproheptadine
  - Antihistamine + Anti muscarine + Antiserotonine.
  - Primary used as appetizer
  - Used in Serotonin Syndrome.
- Methylsergide (Not used)
  - Causes retroorbital & peritoneal fibrosis

Newer drugs – Calcitonin gene related peptide (CGRP)
– Vasodilation.
CGRP antagonist → Olcegepant – i.v.
Telcagepant – Oral
↳ Hepatotoxic

LASMIDITAN – $5HT_{1F}$ agonist

↓

Undertrial

Atypical Antipsychotics
(5HT2 Antagonists)

Clozapine
Quetiapine
Olanzapine
Risperidone
Lurasidone
Ziprasidone
Aripiprazole
Asenapine (S/L)

→ Not causes Metabolic Syndrome

↳ Advantages:
- Less EPS
- Refractory Cases
- +ve & -ve symptoms of Psychosis.

CLOZAPINE – S/E → Agranulocytosis 0.8 – 1%
(dose independent)

Seizure (10%)
Ileus (Paralytic) → Constipation
Sialorrhoea
Metabolic syndrome.
– Pillow ~~wet~~ Syndrome
(wet)
– Anti-suicidal action.

QUETIAPINE – S/E – Cataract, Priapism

OLANZAPINE – USE → Mania in BPD
Adverse effect → Max^{m} wt-gain
Max^{m} metabolic syndrome.

RESPERIDONE: In addition to blocking 5HT2 it also block D_2.
- May cause EPS

LURASIDONE: Useful in BPD
may also cause EPS.

ZIPRASIDONE: M/e S/E – QT Prolongation.

ARIPIPRAZOLE: Useful in BPD (mania)
– Best drug among alypical antipsychotic

ANXIETY DISORDER:
↓ GABA activity
↑ 5HT activity.

BUSPIRONE: 5HT1A agonist
Anti anxiety agent (Chronic Anxiety)
Advantage – Non sedative
Non habit forming.
Disadvantage – Delayed in onset
(3 to 4 wks)

For acute anxiety – Temporarily – BZD

Performance anxiety = Rx: Propranolol
Anxiety & panic attack = Rx: SSRI
H1 blocker: Hydroxyzine (Anti anxiety property)
↳ 1st gen. antihistamine.
Cetrizine → Metabolite of Hydroxyzine
↳ 2nd gen. anti-histamine.

Female Sexual Stimulant : FLIBANSERIN
↓ useful in
HSDD – Hypoactive Sexual desire Order

Deficiency of Serotonin & NE – Depression

TCA, SNRI, NDRI → Inhibit reuptake of 5HT, NE
SSRI → Inhibit reuptake of 5HT.

MAO – inhibitors

MAO-A
- involved in metabolism of NA & 5HT.
- Useful in depression.
↓
Selective MAO-A inhibitor: MECLOBAMIDE, CLORGILINE

MAO-B
- Metabolism of Dopamine
SELEGELINE
RASAGILINE
SAFINAMIDE

Non-selective MAO inhibitors:
PHENELZINE
TRANYLCYPROMINE
ISOCARBOXAZID

Cheeze reaction = T/t : Phentolamine

SSRI:

Fluoxetine (longest acting → 5 to 7 days)
Fluoxamine – Shortest acting
Paroxetine
Citalopram
Escitalopram – Highly selective SSRI
Sertraline – Least drug interaction.

S/E of SSRI – · May cause HTN
– Insomnia, Anxiety, Sexual S/E.
↳ delay in ejaculation.
↓
∴ It is taken in morning.
↓
Useful in t/t of premature ejaculation.

M/c – Nausea & vomitting
– Diarrhoea.

Drug interaction:
Serotonin Syndrome – SSRI + MAO inhibitor
Rx – Cyproheptadine.
↳ Primarily 5HT2 antagonist
Anti H1 + Ach

FLUOXETINE: Least discontinuation Syndrome

PAROXETINE – Wt gain
Teratogenic
Used in Premenstrual tension Syndrome. (PMTS)
↓
FDA approved.

Drug interaction b/w Fluoxetine & Tamoxifen :

Tamoxifen – for anticancer activity needs activation.
– activated ē help of CYP2D6 enzyme.

Fluoxetine – CYP2D6 enzyme inhibitor.

Tamoxifen failure occurs.

SSRI Uses :

① Depression
- juvenile depression – Fluoxetine
Sertraline

② OCD
③ PTSD
④ Bluimia nervosa
⑤ Anxiety ē panic attack.
⑥ PMTS.

DOC : SSRI : ① OCD
② PTSD
③ Anxiety ē panic attack.

TCA
- Inhibit reuptake of Serotonin & NE (Non-selective)

CLOMIPRAMINE – T/t of OCD
DOXEPIN – Strong antihistaminic property
• Atopic dermatitis
• Lichen Simplex

All TCA have antihistaminic property.

IMIPRAMINE – Strong anticholinergic activity.
• Nocturnal enuresis
DOC: Desmopressin
All TCA have anticholinergic activity.

AMITRYPTILLINE
Used in – Antidepressant
Prophylaxis of migraine
DM neuropathy pain
↓
Gabapentin, Pregabalin

Other – Nortryline
Desipramine
Amoxapine – D_2 blocking action
Anti-psychotic
EPS, Galactorrhoea.
Maprotiline
Reboxetine

Adverse effect of TCA:
- All TCA having antihistaminic property
" " anticholinergic "
" " α_1 blocking "

- Sedation, Wt gain, Seizure
↓
∴ taken at bed time.
- Dryness of mouth, constipation, Tachycardia & Retention of urine
- Postural hypotension

TCA poisoning & t/t :
Cardiac arrhythmia → Lidocaine, Brelylium, Avoid Class Ia
Convulsion → Diazepam
Coma →
Metabolic acidosis → i.v. Sodium bicarbonate
- No role of dialysis in TCA poisoning
↳ bcoz large Vd.

Anti-cholinergic
① Avoid TCA in elderly male – Aggravate Urinary Retention.

② Alzheimer's ds.

ST JOHN'S WORT :
Natural antidepressant.
~~EE~~. HYPERFORIN
↳ Monoamine reuptake inhibitor.
- Very powerful enzyme inducer.
↓
lead to OCP failure.
Anti retroviral failure.

MIANSERIN : Presynaptic α_2 inhibitor
Useful in depression.

MIRTAZAPINE : Presynaptic α_2/5HT1 inhibitor
Useful in depression.
- NaSSA (Noradrenergic & specific serotonergic antidepressant).

TIANEPTIN] 5HT reuptake enhancer
AMINEPTIN]

↓

Used as antidepressant

Mechanism of action not known.

BPD (Bipolar Disorder):

Prophylaxis – Lithium

Acute mania – Valproate
Carbamazepine
Olanzapine
Aripiprazole
Diazepam

Depressive phase – Lamotrigine

For Rapid Cycler : DOC : Sodium Valproate

↳ more than 4 episodes of mania & depression in a year.

Lithium: Monovalent cation

Useful for prophylaxis of BPD.

Narrow Therapeutic index (TDM)

↓

Therapeutic drug monitoring

↓

Monitoring plasma lithium level.

↓

$T_{1/2}$ = 24 hrs.

Maintanence for BPD = 0.5-0.8 meq/L

Acute Mania = 0.8-1.2 meq/L

Toxic symptom > 1.5 meq/L

Toxicity → Hemodylasis → 4 meq/L

Adverse effect of lithium:

LI = Leucocyte count ↑ (Leucocytosis)

T = Tremor (M/c → 8-10 Hz)

H = Hypothyroidism (Inhibit release of T_3 & T_4)

IU = ↑ urination (polyurea = DI) (Rx: Amiloride)

M = Mother (Ebstein's anomaly) = Teratogen

In CVS → T wave changes

Dermatology → Exacerbation of psoriasis.

C/I: ① Pregnancy & lactation

② Sick sinus syndrome.

Drug interaction b/w lithium & SMR (Succinylcholine & Pancuronium):

↳ Lithium aggravate the action of SMR.

↳ Stop lithium 1 day before Sx.

Hyponatremia will occur in lithium toxicity.

[Diuretic aggravate lithium toxicity.

[NSAID " " " .

Opioid Receptors.

3 imp. endogenous opioid Receptor in body
- μ (Mu)
- δ (Della)
- k (Kappa)

All opoid receptor are GPCR – via Gi pathway.

Endogenous opioid peptides:
- Endorphine – more affinity toward μ
- Enkephaline – " " δ
- Dynorphin – " " k

Action of opioid:
- Due to activation of μ & δ.

P = Physical dependence, ↑ Prolactin secretion
M = Miosis — NO Tolerance
C = Constipation, convulsion (M3G)
A = Analgesic
R = Respr depression
E = Euphoria
S = Sedation

Opioid are useful in t/t of dull pain
- Continuous pain
- localised pain
- Visceral pain

Opioid (Morphine) activating Edinger westphal nucleus (III CN) causing miosis.
↓
Only systemic Morphine cause miosis.

Action of opioid due to kappa:
D = Dysphoria
M = Miosis
A = Analgesia
R = Resp^{r} depression
D = Diuresis
S = Sedation

Morphine having Histamine Releasing action.
↓
Vasodilation
↓
Shifting of pulm. fluid in systemic circulation.
↓
It is useful for t/t of Pulm. edema.

All the action of morphine may develop tolerance on repeated administration except — Miosis
Constipation
Convulsion

Enkephalins may undergo metabolism by Enkephalinase.
For the t/t of diarrhoea — Racecadotril
↓
Enkephalinase inhibitor.

Pure agonist:
Natural opioid — Morphine, codeine (CYP2D6)
Codeine converted in morphine by CYP2D6 enzyme in body.
Semisynthetic — Diacetyl morphine (Heroin), Pholcodeine

Synthetic — Pethidine (Meperidine — Anti muscarinic,
Nor-pethidine) → Metabolite of pethadi
↓
C/I in t/t MI pain.
↳ S/E — Seizure (convulsion)

Pethidine & Morphine C/I in Renal failure.

Methadone:
- Longest acting opioid
- NMDA blocking property & inhibiting reuptake of NE & 5HT.
- Useful for t/t of neuropathic pain & Cancer pain
- DOC for opioid deaddiction.

Tramadol:
- Also having property of inhibiting reuptake of 5HT & NE.

Be careful using Methadone & Tramadol in pt. using SSRI, MAO inhibitor causing Serotonin Syndrome.

Fentanyl: Fentanyl group.

	Fentanyl	Sufentanil	Alfentanil	Remifentanyl
Potency ↓ potent than Morphine	X100	X1000	X5	X100
Duration of action	30 min	30 min	5-10 min	3-5 min

Least potent: Pethidine & proposyphene (1/10)

Analgesic for day care Sx: Remifentanyl.

Fentanyl + Droperidol = Neuroleptic Analgesia

Fentanyl + Droperidol + N_2O = Neuroleptic anaesthesia.

Fentanyl group Cause Post op truncal rigidity
(Max – Alfentanil)

Thorax muscle rigidity = wooden chest Syndrome.

Mixed agonist – antagonist:

– μ antagonist / kappa agonist:
- Nalorphine (more dysphoria, not in use)
- Pentazocine (Sympathetic stimulant) C/I in MI pain
- Butorphanol (Nasal formulation)

– μ agonist / kappa antagonist:
- Buprenorphine
  - Useful for all type of pain
  - Useful for opioid withdrawl

↓

alternate to methadone.

Pure antagonist:

Naloxone
Nalmefene } Intravenous
Naltrexone (Oral, long acting, Hepatotoxic)

Acute morphine poisoning:

Specific antidote – Nalaxone (0.4–0.8mg)

↓

i.v., repeated every 2-3 min.

– It blocks μ receptor at much lower doses than those needed to block κ or δ receptors.

→ It promptly antagonizes

Naltrexone

→ Useful to control craving for Morphine & craving for alcohol.

For t/t of constipation due to morphine (opioid)
↓
Peripheral opioid antagonist [ALVIMOPEN
                               METHYL NALTREXONE

Newer opioid:
Peripheral Kappa antagonist: ASIMADOLINE
↓
for IBS

Peripheral μ & k-agonist ; delta antagonist:
ELUXADOLINE → for IBS.

Peripheral K-antagonist:
NALFURAFINE → Antipruritic → CKD

Codeine
Dextromethorphan] Anti-tussive opioid.

Anti-diarrhoeal opioid:
Diphenoxylate (Atropine can be added to prevent addiction).
Loperamide

C/I of Morphine:
- Head injury pain (Respr insufficiency)
- Biliary colic pain (causing constriction of sphincter of oddi.)
- Severe asthma.

Ethyl Alcohol / Alcohol :

Deaddiction - Disulfiram like reacⁿ
(Aldehyde dehydrogenase inhibitor)

Drug causing Disulfiram like reacⁿ:

C = Chlorpropamide (Sulfonylurea – DM)
Cefoperazone (3rd gen. Cephalosporin)
M = Metronidazole
Praised = Procarbazine (Anti Cancer) → Alkylated
G = Griseofulvin
T = Tinidazole
Naidu = Nitrofurantoin (Causes coffee colour urine)

Chronic alcoholic generally suffer Thiamine deficiency. (Vit B_1)

Alcohol always undergo Zero order Kinetic elimination:

Zero WATT Power
W = Warfarin
A = Alcohol
A = Aspirin
T = Tolbutamide
T = Theophylline
P = Phenytoin

Excretion of Alcohol – Kidney

In acute ethanol poisoning, pt. presenting c hypoglycemia. T/t = Glucose + Thiamine.

Methyl alcohol:

Methyl alcohol
↓
Formaldehyde
↓
Formic acid (dangerous) < Ocular damage
Metabolic acidosis

Specific antidote for Methanol poisoning
↓
Fomipizole
(4-Methyl pyrazole)
↓
Acting by inhibiting Alcohol dehydrogenase.

Alternative drug – Ethanol also given.
Hemodialysis.

Anti craving drugs for Alcohol:
- Disulfiram (DOC)
- Naltrexone (1st line drug)
- Acamprosate (2nd, NMDA blocker + GABA agonist)
- SSRI (citalapram)
- Ondaselron
- Topiramate, Beclofen (GABA agonist)
- Rimonabant, a CB1 receptor antagonist.

FAS (Fetal alcoholic syndrome):
C/F – Microcephaly
Maxillofadal abnormalities
Movement disorder – Hyperkinetic.
Mental retardation

Phenytoin:
Na^+ channel blocking antiepileptic

Fosphenytoin – Prodrug of phenytoin
Water soluble (im/slow iv)
└safe for┘

Saturation Kinetics – First order → Zero order

Adverse effect:
① Acute toxicity
– On high i.v. → Cardiac arrest.
– High oral → Nystagmus
Ataxia
Diplopia
Vertigo

② Chronic toxicity
– Gum hypertrophy (M/C – 30%)
↳ Due to collagen accumulation
– Blood → Megaloblastic anemia (Folic acid deficiency)
Interfare Vit K activity (Hemorrhage)
Interfare – Vit D & Calcium activity.
↳ Osteomalacia & rickets

- Hypersensitivity reac^{n}
  ↳ Pseudolymphoma.

- In female → Hirsutism
- Inhibits release of insulin from β-cell of pancreas – Hyperglycemia (DM)

- Teratogenicity → due to Areneoxide
  ↳ C = Cleft lip & palate
  P = Hypoplastic phalanges
  M = Microcephaly.

- Extravasation of phenytoin → Purple glove syndrome.

Phenytoin – Microsomal Enzyme inducer.

Non-epileptic uses of Phenytoin:
- Trigeminal neuralgia
- Digoxin – induced VT
- Wound healing

Carbamazapine:
DOC for Partial Seizure (Focal seizure)
For Rt of Temporal lobe epilepsy.

Non-epileptic Uses:
DOC for Trigeminal neuralgia.
Useful for Rt mania in BPD
Carbamazapine having SIADH activity → Antidiuretic
↳ Use in DI

It is microsomal enzyme inducer.
It also undergo auto induction.
↓
Phenobarbitone
Carbamazepine
Neverapine

Sodium Valproate:
- Broad spectrum antiepileptic.

MOA = GABA agonism property
Anti-glutamate "
Na^+ channel blocking "
T-type CCB "

DOC for Myoclonic / Atonic / Clonic & tonic Seizure
First line drug for Absence seizure / Lennox Gestaut Syndrome.

Non-epileptic uses:
- Migraine prophylaxis
- Manic in BPD (LITHIUM)
- Rapid cycler (>4 cycles/year)
- Tardive dyskinesia

It is microsomal enzyme inhibitor

SE: V = GIT, Wt. gain (Vomitting)
AL = Alopecia / curling of hair
P = Pancreatitis, hyperammonia
R = Rashes
Q = PCOD

A = Allergy ← Most
T = Teratogenic (Spina bifida / CVS problem / Orofacial / digital) ← Cleft lip & palate
E = Hepatotoxicity (< 2yrs children).
↓
t/t = Carnitine (Antioxidant)

Others Antiepileptic :
- Levaliracetam (SV2A)
- Magnesium Sulfate (DOC in eclampsia)
- Acetazolamide
- ACTH (Infantile spasm)

Levaliracetam — Modify synaptic release of glutamate / GABA.

Acetazolamide :
- Carbonic anhydrase inhibitor.
- Useful for Glaucoma → Taken Orally.
- Used as diuretics — acts on PCT

Use — Acute mountain sickness
Periodic paralysis
Absence seizures] Rx - GANAXALONE
Catamenial epilepsy]

Absence Seizure :
- Ab⊖ of T-type Ca^{2+} channel (Thalamus)

Rx : T-type CCB
ETHOSUXIMIDE
SODIUM VALPROATE (1st line drug)
TRIMETHADIONE (Withdrawn — Nephrotoxic)
↳ Hemeralopia — Day blindness.

Anti epileptic having Carbonic anhydrase inhibiting property:

TOPIRAMATE] cause Nephrolithiasis
ZONISAMIDE]

RETIGABINE] Potassium channel opener
or EZOGABINE] used for partial seizure
↑ - Causing blue colour pigmentation on lip & skin.
(New drug)

GENERAL PHARMACOLOGY

Pharmacokinetics (PK):

Drug absorption:

Food interfare drug absorption

eg: Milk (Ca^{2+}) — Tetracycline
Protein meal reduces — Absorption of Levodopa.

Food inhances drug absorption
Lithium
Halofantrine
Lumefantrine
Griseofulvin
Bedaquiline
Fibrates — lowering cholesterol
more absorbed ~ cholesterol diet.

- Absorption of Iron↑ — Vit. C (Ascorbic acid)

For a drug to absorb better — Lipid soluble
& distribution. Non-ionised.

Acidic drug non-ionised in Acid medium.
Basic drug non-ionised in Basic medium.
→ Aspirin

Acidic drug – Absorbed in stomach.
Basic drug – Absorbed in Duodenum/Intestine.
→ Morphine

Strongest Acid/Alkali always seen in ionised form.

Heparin – Can't be used orally.
- Heparin ionised molecule, not cross the placenta, so not cause teratogenicity.
↓
DOC – for anticoagulation.

Lignocaine – For rapid absorption/onset of action given c Sodium carbonate.
↓
Weak basic drug. For ↑ duration given c Adrenaline.

Acidic drug poisoning –
For acidic drug poisoning if the pt. is passing acidic urine, you should alkalise the urine.
Urine alkalise c Sodium bicarbonate.

Alkali drug poisoning –
For the Tt of alkali drug poisoning if the pt. passing alkaline urine, you should acidify the urine.
Urine acidify c Ascorbic acid
↓
By injection Ammonium Chloride.

Ion-trapping – Acidic drug (Aspirin) reached basic medium get ionised & trapped in the region.

P-glycoprotein : Permeable efflux pump.
↳ Presence of P glycoprotein decreases the bioavailibity of digoxin.

eg. of P glycoprotein inhibitor : Quinidine
Itraconazole
Erythromycin
Amiodarone
(Verapamil)

Drug undergoing high first pass metabolism on Orally :
Propranolol
Salbutamol
Theophylline
Verapamil
Lignocaine
Nitrates
Imipramine

All nitrates goes extensive 1st pass metabolism except – Isosorbide mono. nitrates.

Rectally given drug absorbed via External hemorrhoidal vein – No 1st pass metabolism
If via Internal hemorrhoidal vein – 1st pass metabolism occurs.

i.v. – 100% Bioavailibility.

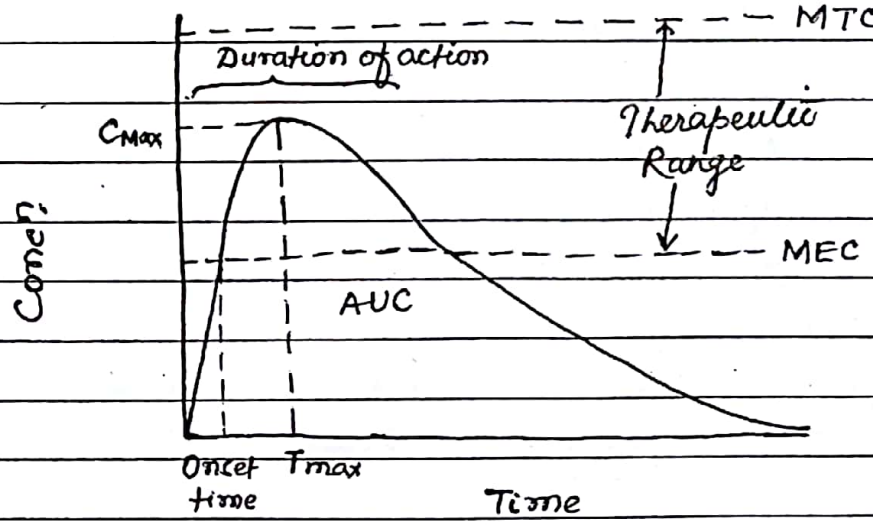
Henderson Hesselbach equation:

$$pKa = pH + \log (\text{ionized A}) / (\text{unionized A})$$

If pKa = pH
means, 50% drugs is in ionised form
& 50% " " unionised form

pKa − pH = 1 ⟶ 90% drug in absorbed form.
pKa − pH = 2 ⟶ 99% "
pKa − pH = 3 ⟶ 99.9% "

Bioavailibility curve:



Cmax = Max^m plasma conc^n
Tmax = Time to reach Cmax
AUC = Area under Curve.

Same drug, same dose, same dosage forms,
< 20% ⟶ Bioequivalent.

Orphan drug:

- A drug useful for diagnosis/prevention & Tt of rare disease.

eg:- Fomipizole (4-methyl pyrazole – Alcohol dehydrogenase inhibitor)
Protamine Sulfate (Antidote of Heparin – Chemical antagonism, 1mg = 100 U of Heparin)
Calcitonin
Digibind (Antidote for Digoxin)
Liothyronine (Active T_3 → Myxodema coma)
↳ always given c β-blocker.

Calcitonin: Useful in Hypercalcemia
Paget's ds
Osteoporosis
diagnosis for Medullary Ca Thyroid.

Pitolisant / Tiprolisant: Use in Narcolepsy (Orphan drug status).

Essential drugs:

- Drug that meet health needs of the majority of population
- Affordable & Available in all area.
- Always single compd.

Schedule H – Drug only given on prescription written by medical practioner (Registered).

Drug distribution:

60% water
70kg → 42L

4L	10L	28L
plasma	Interstitial fluid	Cellular Compartment

If a drug only in the plasma compartment, it is called as low Vd.

If drug is ← Lipid insoluble / Ionised / Highly protein bound / Large size → drug Stays in Plasma Compartment

- Role of Hemodylasis

If a drug goes to cellular compartment it has high or large Vd.

↓

Lipid soluble
Non ionised
Free form.

Large Vd → No role of Dialysis.

Drug can't removed by dialysis :

A = Amphetamine
V = Verapamil
O = Opioids, OPC
I = Imipramine (TCA)
D = Diazoxine
Dialysis = Diazepam (BZD)

BZD — Very strong binding capacity
can't remove by dialysis.

Loding dose depend upon Vd.

For drug having large Vd — for rapid action give loading dose

Volume of distribution (Vd)

$$Vd = \frac{\text{Total i.v. dose}}{\text{Plasma conc}^n/L}$$

Loading dose = Vd × Target plasma conc^n.

Clearance (CL) = Rate of elimination / Plasma conc^n

Maintenance dose = CL × Target plasma conc^n.

$$t_{1/2} = 0.693 \times \frac{Vd}{CL}$$

Plasma protein binding:

- Acidic drug in plasma bind c plasma albumin.

- In nephrotic syndrome or in liver failure (hypoalbuminemia) plasma albumin count is low —
  Use low dose of Acidic drug.

- Basic drugs are generally binds c Alpha$_1$ Acid Glycoprotein

Drug displacement type of drug interaction:

eg: Warfarin displacing tolbutamine from protein binding site.

Sulphonamide displacing bilirubin from protein binding site.

BBB:

BBB absent — Pituitary
Pineal gland
Area Prostrema CTZ
Medain Eminence:

Do not crosses BBB — Streptomycin (Aminoglycosides)
Neostigmine (DOC for Atropine poisoning)
Glycopyrolate (Pre anesthetic medication)
Dopamine

All aminoglycosides are ionised molecule, so never absorbed orally, so not given orally.
Even though aminoglycosides not absorbed in GIT

Neomycin & Parmomycin] can given orally.

Streptomycin – C/I in pregnancy
bcoz it crosses placental barrier & causes permanent deafness.

Redistribution :
eg: Thiopentone Sodium
(Ultra short acting)
↳ Rapidly entering brain & rapidly comes out & distribute to liver, kidney etc.

Biotransformation (Drug metabolism):

Consequences of drug metabolism
① Inactivation (more water soluble)
↓
excreted easily.
② Active metabolite formation from an active drug
③ Activation of inactive drug.

Active metabolite from active drug:

Active drug		Active Metabolite
Phenacetin	→	Paracetamol

↳ causes Analgesic nephropathy so withdraw.

Codiene	→ (CYP2D6)	Morphine

↳ In some people it is deficient.

Diazepam	→	Oxazepam
Spironolactone	→	Canrenone.

Activation of inactive drug

Prodrug	Active metabolite
Levodopa	Dopamine
Methyl dopa	Methyl norepinephrine
Enalapril	Enalaprilat
	└ All ACE i are prodrug except – captopril, lisinopril
Dipivefrine	Epinephrine
Becampicillin	Ampicillin
Minoxidil	Minoxidil Sulphate.
Cyclophosphamide	Phosphamide mustard.

Drug metabolism:

Non synthetic reaction (Phase I reac^n):

1. Oxidation (M/c Phase I reac^n)
   All phase I reac^n taken care by microsomal enzyme – CYP450
2. Reduction
3. Hydrolysis
4. Cyclization
5. Decyclization

Phase II reac^n:

1. Glucuronidation (M/c) – Morphine
2. Sulfate Conjugation
3. Glycine "
4. Glutathione " (Paracetamol metabolism)
5. Acetylation
6. Methylation

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PARACETAMOL

PHASE I / CYP2E1

↓

N-acetyl benzoquino (Hepatotoxic immuno amine (NABQIA) metabolite)

Phase II / Glutathione conjugation

↓

Inactivation

For paracetamol poisoning → [N-acetyl cysteine / Methionine.

↓

Bcoz Glutathione generator.

Chronic alcoholic → More prone for liver damage bcoz Alcohol → CYP2E1 inducer.

End result of phase II reac^{n} → Inactivation.

Drug undergoes Acetylation:

S = Sulphonamide / Dapsone.
H = Hydralazine
I = Isoniazid
P = Procainamide

] may cause RA, SLE.

Methylation:

eg: Histamine → Methylhistamine
Noradrenaline → Adrenaline.

Microsomal enzyme :

Enzyme	Drug
CYP3A4 (M/c)	>50% of drugs
CYP2D6 (2nd)	Codiene → Morphine
Fluoxetine inhibit CYP2D6	
~~Tamoxifen activated by CYP2D6~~	
CYP2C9	Warfarin
CYP2C19	Omeprazole metabolism
	Clopidogrel
CYP2E1	Paracetamol – NABQIA

Clopidogrel : Anti-platelet
Prodrug
Activated c̄ help of CYP2C19.

Aspirin + Clopidogrel (prodrug) –
Aspirin → Causes gastritis
t/t → Omiperazole
Omiprazole shouldn't be given c̄ Clopidogrel.
– Preferred PPI given c̄ clopidogrel
↓
Pantoprazole
Rabeprazole.

Microsomal Enzyme

Inducers:	Inhibitors
G = Griseofulvin	Vit = Valproate
P = Phenytoin	K = Ketaconazole
R = Rifampicin	Can = Cimitidine
S = Smoking	Cause = Ciprofloxacin
Cell = Carbamazepine	Enzyme = Erthromycin
Phone = Phenobarbitone	Inhibition = Isoniazid (INH)
	Grape Fruit

Drug excretion:

Major source = Kidney.

Net excretion of drug = GF + TS − Tubular reabsorption.

✓ PROBENICID — by inhibiting

prolong the action of penicillin.

First order kinetics

- Constant fraction of drug excreted constant interval of time.
- $T_{1/2}$ constant
- 97% drug eliminated after 5 half life.

$100 \xrightarrow[①]{T_{1/2}=1hr} 50 \xrightarrow{②} 25 \xrightarrow{③} 12.5 \xrightarrow{④} 6.25 \xrightarrow{⑤} 3.125.$

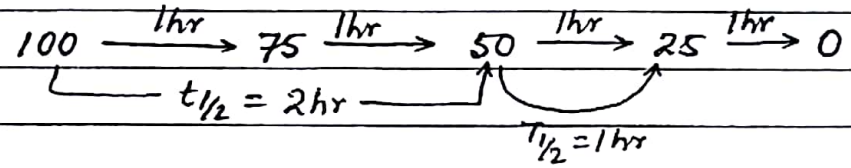
↓

50% of drug excreted every 1hr.

Zero order Kinetics :

- Constant amount of drug excreted constant interval of time.
- No fixed $T_{1/2}$.

eg: 25 mg of drug, every 1 hr.



Common drug undergoing Zero kinetic

Zero WAATT Power

W = Warfarin
A = Alcohol
A = Aspirin
T = Tolbutamide.
T = Theophylline
Power = Phenytoin

Pharmacodynamics :—

Receptor mediated MOA

Cell membr Receptors.

- Ligand gated
  - Fastest acting receptor
- G-protein Coupled
  - Serpentine Shape
  - 7 molecule
  - most active unit of GPCR is d-unit
- Enzyme linked.

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GPCR (α) + GTP → G_s G_i → Adenyl cyclase – cAMP
M2&4 (d_2) (β)

→ Gq → PLC – IP3 + DAG
M_1, M_3, M_5 (d_1)

Enzyme linked receptor :

eg: Tyrosine Kinase Receptor

Insulin acting on cell membr receptor

↓

Activate Tyrosine kinase

↓

Shift GLUT4 from cytoplasm to plasma membr

↓

Influx of glucose.

PEGVISOMENT : GH receptor blocker
Useful for t/t Acromegaly.

New drug → RUXOLITINIB : JAK enzyme inhibitor
Useful in Myelofibrosis.

TOFACITINIB : JAK 1 & 3 inhibitor
Useful in RA.

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Intracellular receptors:

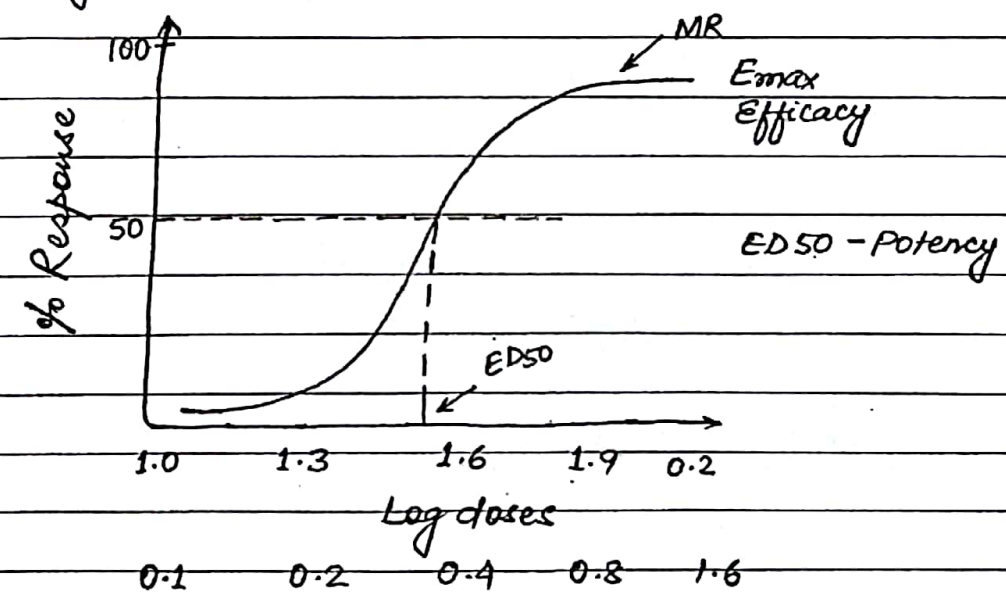
Drug acting on Cytoplasmic receptor:

- Steroid hormone
- Vit D
- Estrogen
- Progesterone
- Testosterone.

Drug acting on nucleus:

- Thyroid hormone

Log dose response curve:



Receptor Antagonism

(1) In the presence of competitive antagonist DRC will be shifted parallel to right.
Efficacy → Same ; Potency → ↓

(2) In the presence of Non-competitive antagonism DRC will just come down
Efficacy → ↓ ; Potency → Same.

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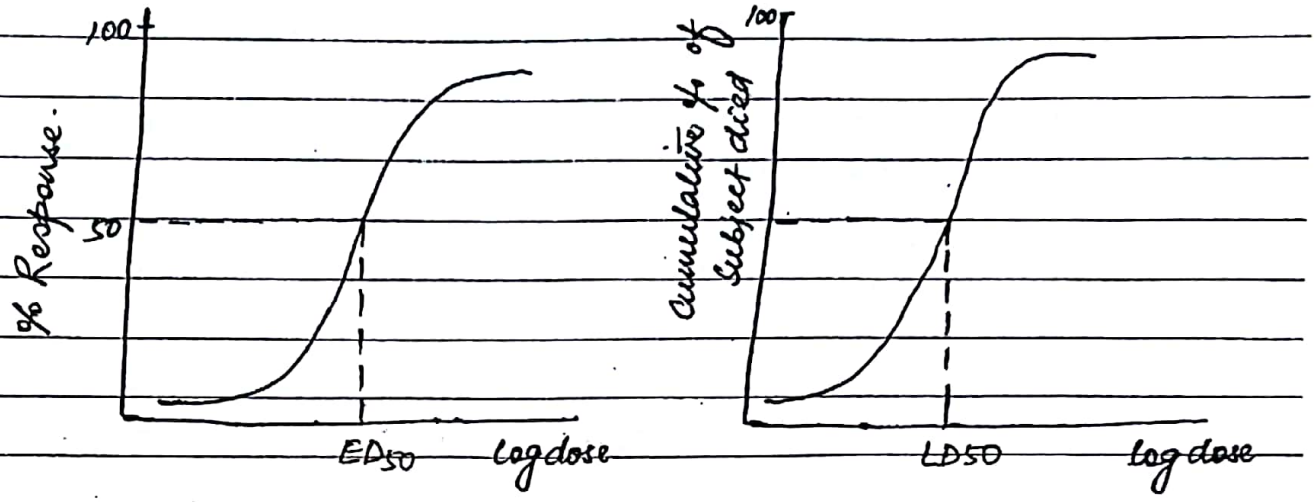
E_{50} & LD_{50}



Lower the ED50 more potent

Lower the LD50 more dangerous drug.

Drug Safety:

$$\text{Therapeutic index} = \frac{LD50}{ED50}$$

Theophylline
Lithium
Anti epileptics
] Narrow therapeutic index.

Warfarin — assessment by INR

$$INR = \frac{\text{Patient Prothrombin (PT)}}{\text{Control Prothrombin}}$$

Heparin — assessment by aPTT

LMWH — No need for monitoring

In obese pt. or Renal failure we do assessment by Anti factor Xa.

Teratogenicity :

Preimplantation (0-2 wks)

Implantation (2-8 wks) → More teratogenicity occurs.
↳ Organogenesis.
Growth & development (9 wks - 9 months)

① Warfarin : causing Contradi Syndrome
(Fetal chondrodysplasia Punctata)

② Isotretinoin (Vit A) - Teratogenic

Lithium — Ebstein Anomaly
C/I in pregnancy.

③ THIOAMIDE :

Methimazole	Aplastic cutis
Carbimazole	Choanal atresia
Propylthiouracil	

↓
Bcoz of strongly binding c plasma protein
less chance of crossing placenta.

④ Alcohol — FAS (Fetal alcohol Syndrome)
⑤ Valproate — Valproate Syndrome.
⑥ ACEi — Renal agenesis
⑦ Indomethacin — Premature closure of ductus arteriosus.
⑧ Cyclophosphamide — Imperforate anus.
⑨ Busulfan & Chlorambucil (Chemotherapy)
— Induce cleft palate

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⑩ Tetracycline — Bone & teeth defect. (Baby)
↓
In mother → Fulminant hepatic failure.

So, definitely C/I in pregnancy.

⑪ Thalidomide — Phocomelia.
↳ Category X drug.

⑫ Misoprostol — Useful for abortion
↳ Teratogenicity → Moebius Syndrome
↓
also ⓐ development of CN VI & VII.

⑬ DES — Female baby → Vaginal Ca (⊂ in 10 yrs of life), hypospadias ↳ Male baby.
↓
If taken in pregnancy.

Drug development:
Preclinical trials — We follow guidelines
↓
CPCSEA = Committee for the purpose of control & supervision on Experiments on Animals.

IAEC = Institutional animal ethics committe.

Clinical trail — Testing on humans.
guidelines — GCP (Good clinical practice).
HEC = Human Ethics committe.

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Phase I : Pharmacokinetics studies
Not efficacy.

Healthy volunteers (20-100)
Open label (No blinding)
- To know maxm tolerable dose (MTD)
MTD - Safety & tolerability.

Anti-Cancer drug by pass Phase I.

Phase II : Therapeutic exploratory
both efficacy & safety.

100-150 patients
Single blind
- To establish therapeutic efficacy.
- Dose ranging & ceiling effect.

Phase III : Therapeutic confirmatory.

Upto 5000 pts, from several centres
Double blind
- To confirm therapeutic efficacy.
- To establish the value of drug in relation.

Phase IV : Post marketing Surveillance.

ethical clearance is not required.
No time limits
To know rare & long term adverse effect.

Phase 0 : Micro dosing studies.

Pharmacovigilence:
- Assessing, ~~monitoring~~.
- Reporting
- Monitoring
- Adverse effect.

Longest acting insulin – Degludec.

Insulin Preparation

Fast onset & Short acting (Onset 10-20 min ; duration-3-4hrs)
- Insulin Lispro
- Aspart
- Glulisine

] For t/t of PP glucose.

Short acting (onset - 30 min ; duration → 5-8hrs)
- Regular Insulin
  - ↓
  - made of 6 molecule (Hexamer)
  - ↓
  - dimer
  - ↓
  - Monomer

] it takes 30 min. to reach monomer status.

given 30 min before meal.
given i.v.
Use in DKA, Hyperkalemia.

Intermediate (Onset 1-3hr ; duration → 16-20hr)
- NPH (Isophane Insulin) – Neutral Protamine Hagedon.
- Lente Insulin (30% semilente, 70% ultralente)

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Longer acting — Glargine (Acidic ⇒ pH=4) (can't mixed c̄ other insulin)
Detemir

Longest acting — Degludec

Adverse effect < Hypoglycemia
Wt. gain.

Inhalable insulin:
EXUBERA - Lack of acceptance by pts & physicians.

AFREZZA - Latest
Ultra rapid (c̄ in 15 min)
FDA approved.

MAO: Insulin acting on cell membr receptor
↓
Activate tyrosine kinase
↓
Shifting of GLUT4 from cytoplasm to plasma membr
↓
Influx of Glucose.

Insulin Release:
For release of Insulin - at least 30% of β-cell are functioning.
In Type I DM - imposible to release insulin
↓
All β cells are destroyed.

Sulphonyl urea
Maglitinide
- Rapaglinide
- Nateglinide

Newer drugs for DM:
GLP-1 analogues:

given S/c
- Exenatide
- Liraglutide
- Taspoglutide
- Albiglutide
- Dulaglutide

S/E - GIT (Nausea, Vomitting, diarrhoea)
Necrotising pancreatitis
Wt. loss.
FDA approved - Liraglutide given for obesity.

- All obtained from GILA MONSTER (Salivary gland Venom).

DPP4 inhibitors: Oral

Adverse effect
- Nasopharyngitis
- URTI.

- Sitagliptine → Excretion: Renal
- Saxagliptine — Renal/Hepatic
- Liraglitpine — Bile
- Vildagliptine — Renal
- Alogliptine.

Vildagliptine: S/E - Hepatic toxicity
pt. undergo periodic LFT.

PRAMLINTIDE: Islet Amyloid Polypeptide analog.
↳ given S/c
↳ Approved for Type 1 & 2 DM..

SGLT2 inhibitors:
- Canagliflozin
- Serligliflozin
- Dapagliflozin
- Empagliflozin

Common S/E – Recurrent UTI (Bcoz Glycosuria)
Risk of breast/bladder CA.

C/I – In Renal failure.

Diabetes – Oral medications.
- Sulphonyl ureas
- Biguanides
- Thiozolidinediones
- Alpha-glycosidase inhibitors
- Meglitinides
- Bromocriptine
- Cholesevelam.

Sulphonylureas

1st generation:
- Tolbutamide (6-12hr)
- Chlorpropamide (30-60hr) – longest acting
  - ↳ causes SIADH (dilutional hyponatremia)

2nd generation:	• Cholestatic • jaundice • Disulfiram like reacn
(Glyburide) Glibenclamide	
Glipizide	
Gliclazide	
Glimepiride	

Glibenclamide — Safe in pregnancy.
Gliclazide — Antiplatelet, antioxidant.

M/c problem of Sulphonylurea — Hypoglycaemia
Wt. gain.

Biguanides: Metformin
MOA = AMPK activator
↳ AMP - activated protein kinase.

Stimulates — Glucose utilisation
↙ ↘
Skeletal muscle | Adipose tissue.
- It is insulin sensitizer.

Supresses — Glycogenolysis
Neoglucogenesis

Useful in T/t of PCOD

Renal root of excretion so C/I in Renal failure.

Stop metformin 1 day before & 1 day after the Radiocontrast exposure.

N acetyl cysteine → t/t of Radiocontrast induced renal cell injury.

Metformin Reduces { Microvascular
Macrovascular events.

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ADR of Metformin : • GI toxicity
• Inhibit intestinal absorption of glucose, hexose, vit B12.

Metformin causes lactic acidosis in presence of kidney, liver or cardiorespiratory failure, alcoholism.

α - Glucosidase inhibitors : inhibit carbohydrate digestion in small intestine.
Acarbose
Voglibose
Miglitol

- Useful in PP blood glucose.

S/E - Flatulance
Abdominal distension
Diarrhoea.

C/I - in Renal failure.

Thiazolidinediones :
PPAR (Peroxisome proliferated - activated receptor)

activation-PPAR α
↓
Stimulate lipoprotein lipase
TGL (VLDL) ↓

PPAR β γ
- Insulin Sensitizer.
• PIOGLITAZONE
Older drugs :
Withdrawn [Troglitazone - Hepatotoxic
Rosiglitazone - CCF

PPAR α agonist : (↓ TG)

- Clofibrate – Not in use (Gall stone, GB malignancy)
- Fenofibrate (Prodrug, longest t½, ↓ LDL, ↓ Plasminogen, Uricosuric action)
- Bezofibrate
- Gemfibrozil

S/E: Myopathy, Hepatotoxicity

M/C S/E Pioglitazone – Wt. gain
Macular edema
Osteoporosis
Anemia
Bladder CA.

Drug activating both PPAR α & γ:
SAROGLITAZAR
↳ Approved in t/t of Diabetes dyslipidemia.

Statins :

HMG CoA + Acetate
HMG CoA reductase ⊖ Statins
Mevalonic acid
↓
Cholesterol ↓

Statins → ↓ Total cholesterol
Statins → ↓ LDL (by upregulation of LDL receptor in liver)

S/E → Myopathy
Hepatotoxic
Teratogenic

Co-enzyme Q given c statins to control muscle weakness.

Liver enzyme goes more than 3 times (N)
- Stop Statins.

COLESEVELAM
↓
Only cholesterol lowering agent in pregnancy.

#

PCSK9 inhibitor:
ALIROCUMAB, EVOLOCUMAB] Monoclonal antibodies for Hypercholesteremia.

Nicotinic acid (Vit B_3) – Niacin
↓ LDL
↓ LP(a)
↑ HDL
S/E – Cutaneous flushing → (Niacin promotes the synthesis of vasodilatory PGs)
↓
So, Aspirin added c Niacin to control flushing.
Hyperuricemia
Diabetes (causing Insulin Resistance)
Hepatotoxicity

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EZETIMIBE : inhibit cholesterol absorption in intestine.

Bile acid Sequestrants :
- Cholestyramine
- Colestipol
- Colesevelam
  - ↳ approved for t/t of DM.

MIPOMERSEN : Newer drug
Given S/C Once in a week.
Useful for lowering cholesterol.

PROBUCOL : Inhibits LDL oxidation

GUGULIPID : ↓ LDL (Not use – Diarrhoea)

CETP inhibitors : (Cholesterol ester transport protein)
TORCETRAPIB
Dalcetrapib
Evacetrapib
Anacetrapib.

MTP inhibitor (Microsomal triglyceride transporter protein inhibitor)
LOMITAPIDE

AVASIMIBE : Inhibit conversion cholesterol to cholesterol ester.
ACAT-1 inhibitor.

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Antithyroid drugs:

Histology of thyroid gland –

Steps of Synthesis:

1. Iodide uptake
2. Oxidation of iodine & formation of Iodine
3. Organification (Iodine + Thyroglobulin)
4. Coupling — MIT + DIT = T_3
   DIT + DIT = T_4

T_3 & T_4 Stored in follicle for 3-4 days.

THIOAMIDES:

- Propylthiouracil (also inhibit peripheral conversion of $T_4 \rightarrow T_3$) → Rapid control of hyperthyroidism
- Carbimazole (Prodrug)
- Methimazole

→ active form

- inhibit synthesis of T_3 & T_4
- inhibit formation of new thyroid hormone
- lag period of 1-3 wks.

M/C S/E of Carbimazole & Methimazole : Maculopapular rash (4-6%)

Agranulocytosis (0.1-0.5%)

* Severe Hepatitis – PTU

Causing teratogenicity – Fetal aplastic cutis
Choanal atresia.

Hepatotoxic – PTU

PTU – Used in emergency hyperthyroid crisis.
– may be safe in pregnancy

LUGOL's IODINE :

MOA – Inhibits release of T_3 & T_4 from follicle.

- Fastest acting antithyroid drug.
- Used in post-op preparation.
- Reducing vascularity.

S/E – Iodism – Acne form skin rash.

Peripheral conversion of $T_4 - T_3$ inhibitor:

β-Blockers
Amiodarone
Propyl thiouracil
Dexamethazone
Ipodate

} By inhibiting 5-DE Iodinase.

Iodide uptake inhibitor :

POTASSIUM PERCHLORATE
THIOCYANATE

- Used in t/t of iodide induced hyperthyroidism.

Radioiodine therapy :

I^{131} → $t_{1/2}$ = 8 days
↳ emits 2 rays < γ, β

Penetrating power = 0.5 – 2mm.

γ-Ray useful for diagnostic purpose
β-Ray " " therapeutic "

C/I – Pregnancy, Young children, Ophthalmopathy.
Not useful for t/t of Medullary Ca thyroid.

Newer drug for T/t of Medullary Ca thyroid:
LENVATINIB – DTC
VANDETANIB – MC

Non-thyroid drug causing Hypothyroidism:
LITHIUM (Stop release of T_3 & T_4 from follicle)
AMIODARONE] (inhibit conversion of $T_4 \rightarrow T_3$)
PROPRANOLOL]
ETHIONAMIDE] inhibit synthesis
PAS]
SODIUM NITROPRUSSIDE – inhibit uptake of Iodide.

Growth Hormone Release inhibitor
– for t/t of Acromegaly
OCTREOTIDE] S/C
LANREOTIDE]

GH Receptor inhibitors –
PEGVISOMANT – S/C

D_2 analogue –
BROMOCRIPTINE] oral
CABERGOLINE]

Octreotide – 40 times more potent than Somatostatin
longer acting – 12hr.
Given (S/C) or i.v.
Never orally.
Uses – Acromegaly
Carcinoid [Diarrhoea]
AIDS
Portal HTN (Bleeding esophageal varices)

S/E – Gall stone
Vit B_{12} deficiency (Megaloblastic anemia)
Rarely DM also.

Dwarfism : T/t
GH releasing factor analogue :
SERMORELIN
HEXARELIN
TESAMORELIN
↳ For lipodystrophy in HIV pt.
↓ Abdominal fat.

GH analogues
SOMATREM] also used in – AIDS related wasting
SOMATROPIN] Turner Syndrome.
Pituitary dwarfism.

S/E – Insulin resistance – Type 2 DM
↑ ICT.
↳ To rule out Papiledema
→ Fundus exam^{n}

Analogue of IGF + IGF binding protein 3
MECASERMIN (S/c) ↓
to maintain stability.

S/E – Hypoglycemia

Uterus : OXYTOCIN
- ↑ force / frequency of contraction.
- ↑ contractility to fundus & body, lower segment not contracted unlike ergometrine & methyl ergometrine.
- Useful in induction of labour.

Control post partum hemorrhage
Useful in ejection of milk.

ATOSIBAN – Oxytocin Receptor Antagonist.

Tocolytic of choice in heart ds – $MgSO_4$

ZOLENDRONATE – Bisphosphonate given i.v.
once in a year
DOC for postmenopausal osteoporosis.

NATALIZUMAB – Useful for Multiple sclerosis
given once in a month.

MIPOMERSEN – ↓ cholesterol level
given s/c once in a week.

DALBAVANCIN – Glycopeptide
Antibiotics
Give once in 6-10 days.
Single dose act 6-10 days

Drugs for Osteoporosis

Drugs inhibit Osteoclast:

- Bisphosphonates
  - ↳ DOC: Zolendronate
- Estrogen & SERM
- Cinacalcet
- Calcitonin
- Thiazide diuretics
- Denozumab - Rank L antibody.
  - ↳ Monoclonal antibodies

Drugs promoting osteoblast:

- Calcitriol (Active form of Vit D)
- Androgens & Anabolic steroids
- Calcium
- Parathormone
  - (hPTH 1-34) → teriparatide.
    - ↳ PTH analogue
    - given only for 1yr (Max^{m} 2yr)
    - long term therapy cause Osteosarcoma.

STRONTIUM RANALATE

- ↳ Dual action < promoting osteoblast
  - inhibiting osteoclast.

ZOLENDRONATE:

- Anti osteoclastic activity
- Interference on mevelonate pathway - antitumour activity (CML)
- Faster acting.
- DOC in Hypercalcemia (osteonecrosis of jaw.
- Also used in Paget's ds.

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- Less venous irritant
- Renal toxicity.

S/E - • Thrombophlebitis
- During infusion fever + chills "Infusion reac" "
• Nephrotoxicity.
• Osteoporosis of jaw bone.

M/c drug for • steroid induced osteoporosis - Bisphosphonate.
Osteonecrosis of Neck of femur - S/E of steroid.

STEROIDS:

1. GLUCOCORTICOIDS:

CLASS A → Short acting (Duration < 12hrs)

	Gluco	Mineralo
Max^m mineralocorticoid activity → Hydrocortisone	1	(1)
Cortisone (least potent G)	0.8	0.8

CLASS B → Intermediate acting (duration 12-36 hrs)

Prednisone	4	0.8
Prednisolone	4	0.8
Methyl prednisolone	5	0.5
Triamcinolone	5	0
Deflazacort	5-6	0

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CLASS C : Longer acting (> 36 hrs)

Paramethasone	10	0
Betamethasone (Most potent G)	25	0
Dexamethasone (Maxm G)	30	0

Mineralocorticoids :

- Natural.

Aldosterone	0	3000

- Synthetic

DOCA	0	20
Fludrocortisone	10	250

Maxm glucocorticoid action — Dexamethasone
Maxm mineralocorticoid action — Aldosterone
G c max min — Hydrocortisone
Least potent G — Cortisone
Most " " — Betamethasone
Maxm topical action — Triamcinolone
Selective glucocorticoid (No mineralo) — TPDB
Selective Mineralocorticoid (NO Gluco) — DOCA

Steroid — Anti inflammatory
Anti cancer
Immunosuppressive

Anti-inflammatory action of steroid
- By inhibiting Phospholipase A_2

ZILEUTON — inhibit lipooxygenase
Not in use
Severe. hepatotoxic
NSAID — Inhibit Cyclooxygenase.

Steroid having anti-cancer activity:
- Apoptosis of T & B cells
- Useful for Lymphoma.

Steroid having Immunosuppressive action:
- Inhibit IL-1 & IL-6
- Also catabolism of IgG.

Methyl prednisolone — Used in pulse therapy.

ACTH
Cosyntropin — Infantile Spasm.

Adrenal cortex → Medulla – Pheochromocytoma
Adrenal cortex – Cushing Syndrome

Drug useful for t/t of Cushing Syndrome:
- Metyrapone (11β-hydroxylase)
- Ketoconazole
- Mitotane
- Aminoglutethimide
  ] – Chemical adrenalectomy
- Trilostane
- Etomidate (General anesthetic)

PASIREOTIDE – Somatostatin analogue
useful in t/t of Cushing Syndrome.

Erectile dysfunction:

① Selective PDE5 blocker:
- Sildenafil
- Vardenafil
- Tadalafil – longest acting
- Avanafil

- PDE5 enzyme is involved in metabolism of CGMP.
- PDE5 blocker by blocking CGMP metabolism causes vasodilation.

Acute adverse effect – Headache
Flushing
Hypotension
Nasal congestion

Long term (chronic) therapy causes Blue vision defect.
↓
blocking PDE6

Drug interaction b/w Sildenafil & Nitrates:
Nitrates shouldn't be given c̄ Sildenafil bcoz risk of severe hypotension.

Other drug for erectile dysfunction:
Apohorphine (D4 agonist)
Trazadone (Atypical antidepressant)
Avaptadil (VIP – Vasoactive intestinal polypeptide)
Ketanserin (Serotonin antagonist)
Naltrexone (Opoid Antagonist)
~~Gingseng~~ Ginseng
Kava
Gingko

Injectable therapy for Erectile dysfunc^{n}:
Alprostadil
Phentolamine
Papaverine.

Drugs useful for t/t – Premature ejaculation.
- SSRI
- PDEV inhibitors

For delayed orgasm:
Amantidine
Buspirone
Cyproheptadine.

For sexual stimulation:
- Yohimbine
Zinc
Ginkgo biloba
~~Gingseng~~ Ginseng.

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ANTI ANGINAL DRUGS

Stable Angina
Unstable Angina
Vasospastic angina (Prinzmetal Angina) (variant angina)

Cause < Reduction in O_2 supply
↑ O_2 demand.

Anti-anginal drugs

Vasodialator — Nitrates, K^+ channel opener; CCB

Cardiac depressant — β-blocker

Pathway of FA oxidation inhibitors (pFox)

\# Fatty acid
↓ oxidation ← ⊖ TRIMETAZIDINE, RANOLOZINE
Free radical
↓
Cytotoxicity to myocardial cell.
Angina, Arrhythmias

TRIMETAZIDINE, RANOLOZINE → Anti-oxidant
~~Na^+ channel blocker~~

S/E – GI toxicity (M/c)
Thrombocytopenia
Liver dysfunc^n
Risk of movement disorder – C/I in Parkinsonism
QT – ~~prolongation~~ prolongation –
Excretion by Renal pathway – C/I in Renal failure

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NITRATES

Short acting	Intermediate acting	Long acting	Longest acting
• GTN	• Isosorbide dinitrate (2-3 hrs)	• Isosorbide mononitrate (6-10 hrs)	• Pentaerythritol tetranitrate (8-12 hrs)
• Amyl Nitrite (Shortest)			

For acute attack – GTN, Isosorbide dinitrate
S/L

Least 1st pass metabolism – Isosorbide mononitrate.

S/L drug – Lipid soluble
Non ionised

Sk in rasher – Pentaerythritol tetranitrate

MOA of nitrates:
– Nitrates acting on Cisteine receptor, they release NO. NO activate Guanyl cyclase.

↓ ↓

Vasodilation ⊖→ CGMP (2nd Messenger)

⊖→ PDES ↓

Sildenafil SMR

NO independent – direct Guanyl cyclase activators:
RIOCIGUAT
CINOCIGUAT
– Useful for t/t of Primary pulm. HTN.

CGMP normally undergo inactivation by PDES enzyme.
So, PDES inhibitor = Sildenafil group of drug.

Nitrates may get tolerance due to down regulation of receptors.

Maxm Tolerance — i.v. infusion
& Transdermal patches.

Action of Nitrates :

Visceral smooth muscle — Relaxed
↳ Useful for t/t of Biliary colic pain
↳ Useful for t/t of Achalasia cardia

Vascular smooth muscle — Vasodialator
↓
predominantly Venodialator
- Peripheral pooling of blood
↓
maxm ↓ in Preload.
mild ↓ of afterload.
↓
↓ O2 demand
↓
Reduce angina.

Uses : Cardiac uses : Angina
MI
CCF

Non-cardiac uses : Biliary colic pain
Achalasia cardia
Cyanide poisoning.
↳ By formation of Methemoglobinemia.

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ADR – Throubing Headache (M/c)
Hypotension
↳ Reflex Tachycardia (due to Sympathetic stimulation)
↓
So add β-blocker.
Tolerance
Methemoglobinemia
Rashes

Drug interaction b/w Nitrates & Sildenafil :
– Not combined together bcoz it cause severe hypotension.
Gap of 8–10 hrs should be maintained.

Sodium Nitroprusside :
– Only i.v. route
– Short acting <10 min
Indication – Hypertensive emergency.
Acute aortic dissection.

– Drug is sensitive to light
↳ cover c black towel.
– Containing cyanide (Thiocynate)
↓
Risk of Hypothyroidism
– C/I in pregnancy.
–

β-blockers :
• ↓ Work load of cardiac.
• C/I in variant angina.
• Abrupt withdrawal ppt. angina.
• β-blocker + GTN = to prevent Reflex Tachycardia.
• Controls catecholamine activity
↓

Role of β-blocker on MI :

Reduces size (zone) of infarction
Anti arrhythmic action
Reduces mortality.

CCB :

Chemical Type	Chemical names
Phenylalkylamines	Verapamil
Benzothiazepines	Diltiazem.
1,4-Dihydropyradines (DHP)	Nifedipine Nicardipine Nimodipine Amlodipine Nitrendipine (NO releasing property)

Nevibolol, Nepradiol] β-blocker having NO releasing property.

DHP :

Site of action – Peripheral blood vessel
↓
Vasodilatation
– Useful for t/t of HTN & PVD.

↳ Maximally arterial dilatation.
↳ maxm ↓ in PVR.

ADR → Hypotension
Reflex Tachycardia
Ankle edema (Amlodipine maxm cause Ankle edema)
Constipation

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Nicardipine (long acting)] Approved in Hypertensive emergency.
Clevidipine (short acting)] given i.v.

Non-dihydropyridines: Verapamil
Diltiazem.

Verapamil:
Site of action: AV node (Most imp.)
SA node

Action → Bradycardia
→ Anti arrhythmic agent.

Uses – Atrial Tachyarrhythmia (AT)
SVT (Supra Ventricular Tachyarrhythmia)

ADR – Bradycardia
Block AV conduction – Prolongation of PR interval.
Ankle edema
Constipation

C/I – WPW syndrome.

Diltiazem:
Uses – HTN
Angina
Arrhythmias (SVT/AT)

CCB having anti-arrhythmic property < Verapamil] class IV antiarrhythmic
Diltiazem]

Nimodipine: Cerebro-selective CCB
Useful for t/t of Sub-arachnoid hemorrhage (SAH)
↓
The purpose of given Nimodipine is to prevent Reflex ischemic brain damage.

≡ FASUDIL – Rho Kinase inhibitor
Use – SAH
PHT (Pulm. HTN)
Angina.

CCB useful in Prophylaxis of Migraine – Verapamil
Flunarizine
↓
T-type of CCB
Na^+ Channel blocker
Anti-oxidant.

K^+ channel openers:
Hydralazine, Minoxidil, Diazoxide – Arteriolar dilator – Anti-hypertensive

Nicorandil (Anti-anginal)

Adenosine (PSVT) → DOC

Nicoraudil: NO releasing property
Anti-anginal
S/E → Aphthous ulcer
Headache

Hydralazine :
- T/t of HTN-emergency in pregnancy
- NO releasing property
- Metabolism by Acetylation

S = Sulphonamide
H = Hydralazine
I = Isoniazid
P = Procainamide.

- Cause RA/SLE

Minoxidil :
- Prodrug
- Active form → Minoxidil Sulphate.

Uses → HTN
Alopecia

Diazoxide :
- causing hyperglycemia by inhibiting insulin release from β-cell of pancreas.

Use - HTN
Insulinoma.

Phenytoin - also inhibit release of insulin.
Poor man drug for Insulinoma.

IVABRADINE -
- Causing Bradycardia.
- Na^+ Channel blocker (Funny Current)
- Reduce HR.

Invo indication < CCF
Angina.

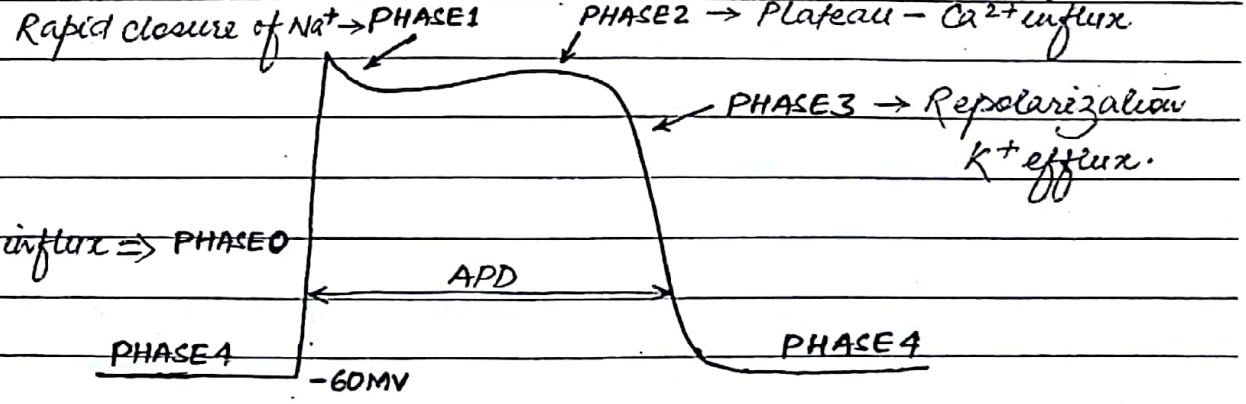
S/E - On chronic therapy — Causes Luminous phenomena.
(Visual disturbance)

Hemoralopia - Trimethadione (Withdrawl - due to Nephrotoxicity)
↓
Day blindness

Reperfusion - Thrombolysis / PTCA

Drug eluting Stent:
SIROLIMUS (Immunosuppressant)
PACLITAXAL (Anti cancer drug additional immunosuppressant)
↓
used c stent to decrease rejection.

ANTI-ARRHYTHMIC DRUGS:



PHASE 3 → T WAVE
PHASE2 → ST segment
PHASE 0,1 & mid phase of 2 → QRS
APD (Action potential duration) → QT interval.

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Any drug having K^+ channel blocking property
— Cause QT prolongation

- Class Ia & class III drug having K^+ channel blocking property causing QT prolongation.

Classification : Vaughan Williams
Class I - Na^+ channel blocker
↳ Class IA, IB, IC
Class II - β-blocker

Class III - K^+ channel blocker.

Class IV - CCB

Unclassified & Miscellaneous agent
↓
Adenosine
Atropine
Digoxin
Magnesium Salfate
KCl

Class IA :
- Block Na^+ channel + K^+ channel block
- Having risk of causing QT prolongation.

Eg: Quinidine
Procainamide
Disopyramide.
] Anti vagal action

Quinidine –

Origin – Cinchona bark

↳ Symptom – [redacted] Cinchonism

↓

Tinnitus

S/E → Diarrhoea

Hypotension (Bcoz α blocking property)

Hypoglycemia (Bcoz Insulin releasing property)

SMR

Thrombocytopenia.

Drug interaction: Quinidine + Digoxine

Quinidine interfare renal excretion of Digoxin.

∴ aggravating plasma level of Digoxin

↓

∴ Digoxin toxicity.

Procainamide:

S/E – Undergo metabolism by Acetylation

SLE.

Disopyramide:

Highest anticholinergic action.

Dry mouth, constipation, Retention of urine.

↓

Not safe in elderly male c BPH.

Class IB:

Na^+ block + K^+ opening.

– Never causes QT prolongation.

Site of action → Mainly acting on Bundle of HIS.

Rt. Bundle, Lt. Bundle & purkinje fibre.

Used only for t/t → Ventricular arrhythmias (Tachycardia)

eg: Lignocaine (Lidocaine)
Mexiletine
Phenytoin
Tocainide.

Mexiletine:
- Lignocaine derivative
- Useful for t/t Ventricular arrhythmias.
- Used for Diabetic neuropathy pain (Unlabeled Use)
- Used for Phantom limb pain

ADR - Severe Nausea & Tremor.

Phenytoin:
- Antiepileptic

USE - t/t of Digitalis (Digoxin) induced VT

Tocainide:
Bcoz of causing Agranulocytosis it is not used.

Lignocaine:
- Class IB drug
- Never given orally bcoz undergo extensive 1st pass metabolism
- Given i.v.
- Lipid soluble, Cross BBB.

S/E - Convulsion
↳ Sign - Nystagmus (1st sign)
1st Symptom - Circum oral paresthesia

Use — VT (Ventricular Tachycardia)
VF (Ventricular Fibrillation)
Digoxin induced VT (DOC: Lignocaine)

↳ # Class IB drug has no role in atrial arrhythmias

Class IC:
- Na^+ blocking + Negligible effect on K^+ channel.
- Maxm pro-arrhythmic property.
- Non commonly used.
- Only for [redacted] antiarrythmic drug causing arrhythmia.

Flecainide (DOC: for Acute WPW)
Encainide
Propafenone
Moricizine

PROPAFENONE:
- Also β-blocking property.

Class III: K^+ channel blocker
- Prolong APD → QT prolongation

AMIODARONE:
- Iodine containing anti-arrhythmic drug.

Multi MOA: · K^+ channel blocking
Na^+ channel blocking
β-Blocker property
CCB property.

∴ Broad spectrum Anti-arrhythmic.

Half life = 53 days.

USES : All type of arrhythmias
Ventricular & Supraventricular arrhythmias.

ADR :

PLz = Photosensitivity, Pigmentation of skin (Gray-blue)
Check = Corneal deposition (Whorl like pattern cornea)
PFT = Pulm. fibrosis, Peripheral neuropathy.
LFT = Liver damage, Pseudo alcoholic liver injury & Mallory hyline bodies.
TFT = Hypothyroidism
- due to inhibition of peripheral conversion of $T_4 \rightarrow T_3$
Hyperthyroidism

Whorl like pattern cornea — Cornea verticillata or Vertex Keratopathy.

[Pseudo lymphoma — Phenytoin
Pseudo jaundice — Rifabutin

Amiodarone causing Hyperthyroidism due to :
Hypothyroidism : inhibition of peripheral conversion of $T_4 \rightarrow T_3$.
Hyperthyroidism
① Contain Iodine → Iodine help in synthesis of T_3 & T_4
② Can cause inflammation of follicle.

In each 200mg tablet there is 75mg of iodine.
Rx : Inhibit iodide trapping
• Perchlorate
• Thiocyanate.
For inflammation — Rx : Dexamethasone (Steroids)

Class III drugs:
- Amiodarone
- Dronedarone (Noniodine)
- Bretylium (Chemical defibrilator)
- Sotalol
- New drug: Dofetilide
- New drug: Ibutilide (FDA approved for conversion of AF-SR) — i.v.
- New drug: Vernakalent

Class IV: CCB
- Verapamil (Most potent)
- Diltiazem

Miscellaneous drugs:

ADENOSINE:
- Given i.v., short acting, Rapid infusion (Bolus)

Site — Close to heart.
- DOC for SVT
- It is also called Endogenous epileptic.

Antagonist — Methyl xanthine - theophylline

Agonist — Dipyridamole
Cause ↳ Coronary Steal Phenomenon.

For Acute SVT: i.v. Adenosine
i.v. Verapamil.
↳ Prefer in Asthma & SVT.

To prevent recurrance of SVT: Oral β-Blocker
Oral Verapamil.

$MgSO_4$:

USE → ① CNS

↳ Long QT syndrome

Congenital	Acquired.
β-blocker (Propranolol)	$MgSO_4$

USE: ↳ Digitalis intoxication

↓

Hypokalemia
Hypomagnesimia → Give $MgSO_4$
Hypercalcimia

② Respr System
USE : Bronchial asthma

③ GIT (laxative property)
USE : Constipation.

④ Ortho (anti inflammatory property)
USE: Synovitis.

⑤ Obs. & Gyn.
USE: Eclampsia.

S/E – Diminished deep tendon reflex (M/c)
Rarely Respr failure.

Safety limit – 4m Eq/L
If >7m Eq/L → Patellar reflex ↓
>14m Eq/L → Respr failure.

Antidote — Calcium Gluconate.

ATROPINE:
- Anti-cholinergic agent.
- Causing Tachycardia.

USE — Bradycardia or Heart Block.

DIGOXIN: Already discuss

Cardiac glycosides:

	Digoxin	Digitoxin
T1/2	40hrs	5-7 days
Route of excretion	Renal	Hepatic
Plasma conc^{n}	0.8-1.5 ng/ml	15-30 ng/ml.

- Both have narrow therapeutic index i.e. Unsafe & need monitoring.

Digoxin S/E: Non-Cardiac S/E
- Nausea & Vomitting (M/c)
- CNS depression
- Yellow vision defect (Xanthopsia)
- Gynaecomastia (In male)

Cardiac S/E
- Atrial Tachyarrhythmia (AT)
- AV block
- VT (Ventricular Tachycardia)
- Ventricular Bigeminy (M/c)
- Non-paraxysmal AT & Variable AV block
  ↳ Most characteristic arrhythmia.

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For t/t digoxin induced AT — Propanalol.

Atropine → AV Block.
Lignocaine → VT

No role of Hemodylysis in digoxin toxicity bcoz large Vd.

Antidote for digoxin toxicity — Digibind.
↓
Check S. K^+, Mg^{2+}, Ca^{2+}

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DIURETICS.

In the PCT → Carbonic anhydrase
↓
Reabsorption of $NaHCO_3$ (85%)
Reabsorption of NaCl from urine (60%)

Thin descending limb — Absorption of H_2O
↳ Concentrating Segment

Thick ascending limb → $Na^+ - K^+ - 2Cl^-$ Symporter
↓
Absorption of $Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}$.
(Diluting segment) (25%)

DCT → $Na^+ - Cl^-$ Symporter
↓
Reabsorption of NaCl (10%)
Reabsorption of Ca^{2+} (+PTH)
↑
c help of

CT → Reabsorption of NaCl (c help of aldosterone) (5%)
Secretion of K^+ & H^+
Reabsorption of H_2O (c help of ADH)

Primary Hyperaldosteronism (Conn's Syndrome):
↑↑ Aldosterone
C/F – HTN
Hypokalemia
Metabolic alkalosis.
For t/t HTN → K^+ sparing antidiuretic
↳ Spironolactone.

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Carbonic anhydrase inhibitors:

Acetazolamide
Dorzolamide
Brinzolamide
} Non-competitive & Reversible.

Site of Action – PCT
MOA – Inhibit Carbonic Anhydrase.

ADR – ① Loss of HCO_3^- → Metabolic acidosis.

Acetazolamide causing Alkaliurea
↳ So used in Alkalation of urine.

② Max^m potassium loss.

CA inhibitor also acting on collecting duct – it inhibit tubular secretion of H^+ → so cause Metabolic acidosis & massive Hypokalemia.

CA inhibitor are Sulpha derivative:
SE – Hypersensitivity
Bone marrow suppression.

C/I – liver disease (hepatic encephalopathy)
COPD
Metabolic acidosis.

Loop Diuretics : High ceiling diuretic (↑ dose → ↑ diuretic action)

site of action : Thick ascending loop of Henle

↓

MOA : Inhibiting $Na^+ - K^+ - 2Cl^-$ symport

↓

loss of Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}

Eg : Furosemide → Vasodilatory action (USE : RF, LVF)

Bumetanide → Most potent

Mersalyl → Kidney damage (Not in use)

Ethacrynic acid → Highly ototoxic (No CA enzyme inhibition)

Torsemide → Longest $t_{1/2}$

Role of Furosemide in Renal failure :

Furosemide promote the synthesis of vasodilatory PG

↓

By ↑ intra renal blood supply

↓

Improving Renal failure

NSAID + Furosemide → NSAID is not given c Furosemide in Renal failure pt. bcoz it inhibit synthesis of PG.

Diuretics of choice in the presence of RF

Choice – Furosemide

ineffective – Thiazides

Exception – Metolazone

C/I – K^+ sparing drugs.

Role of loop diuretics in heart failure:

Furosemide – Only Relief symptoms of CHF.
↓ diuretic action
Main mech^ : Vasodilation
↓
Bcoz of vasodilation furosemide (i.v.) rapidly relief breathlessness in CHF.

S/E of loop diuretics:

Water loss	Electrolyte imbalance	Metabolism	Miscellaneous.
Profound ECFV Depletion	Loss of Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+} ↓ Calciurea (Risk of kidney stone)	(Hyperuricemia) Hyperglycemia Hyperlipidemia. ↓ Exception: INDACRINONE (Ethycrinic acid derivative) ↓ Uricosuric agent.	Metabolic alkalosis Ototoxicity (Irreversable) → Other drugs: Aminoglycosides Cisplatin Vancomycin Erythromycin

Drug interaction: Loop diuretics + Arrhythmia
– loop diuretics by causing hypokalemia & hypomagnesimia → causing digoxin toxicity.

Thiazide diuretics:

Site of action : DCT

MOA : ① Inhibiting $Na^+ - Cl^-$ Symport.

② Promotes Reabsorption of Ca^{2+}

↓

Causing hypercalcemia (Urine Ca^{2+} ↓)

↓

Safe for Renal stones.

③ Also having antidiuretic activity.

eg: Indapamide → Vasodilatory action (No CA enzyme inhibition)
Chlorthalidone → longest acting
Metolazone → Useful even in severe RF.

A/c to JNC guidelines, the 1st line drugs are:

Thiazides - type diuretic
CCB
ACE inhibitors
ARB's

Therapeutic effect:

As a diuretic — ① T/t of Mild edema
② T/t of HTN

As a anti-diuretic — T/t for Nephrogenic DI.

If ↓ Ca^{2+} Excretion → Idiopathic hypercalciuria or William Syndrome
→ T/t of Calcium Nephrolithiasis

Adverse effects:

Water loss	Electrolyte abnormality	Metabolism	Miscellaneous
ECFV depletion	Hypokalemia Hyponatremia Hypercalcemia ↓ Use in t/t: Osteoporosis	Hyperuricemia (Hyperglycemia) ↑ LDL ↓ Thiazide causing insulin resistance as well as inhibiting Insulin release ↓ HTN c̄ Hyperlipidemia (So don't use thiazide)	Metabolic alkalosis Impotency (Erectile dysfunc^n) ↑ β-blocker also

K^+-Sparing diuretics

Aldosterone antagonist
- Spironolactone (M/c) ←
- Canrenone (Active metabolite)
- Eplerenon (No gynaecomastia)
- Drospirenone (Progesterone)

ENa channel inhibitor → Causing Hyperkalemia.
- Amiloride
- Triamterene.
- Pentamidine
- Trimethoprim.
  - → Anti-microbial having ENa channel inhibitor property.

ENaC:
- Na^+ from urine in CD is absorbed by ENaC.

Spironolactone:

MOA: One & only drug acting on interstitium.

MOA of Amiloride: Amiloride acting from lumen & blocking ENaC.

Therapeutic uses of Spironolactone:

↓

Blocks Aldosterone

1. T/t for Primary Hyperaldosteronism (Conn's)
2. (DOC) T/t for Edema of liver cirrhosis (Ascites)
3. T/t for Heart failure.

Disease modifying HF → Spironolactone.

Adverse effects:

(M/C) < Hyperkalemia
Metabolic acidosis.

Long term effect in male – Impotence, Gynecomastia ← Beos of Anti androgenic action.

in female – Menstrual irregularities.

Drug causing Gynecomastia:

D = Digoxin
I = INH
S = Spironolactone
C = Cimetidine
K = Ketoconazole
O = Oestrogen / anti-androgen → Finasteroid

↓

T/t of male pattern baldness.

Drug useful in painful Gynaecomastia — Tamoxifen. (DOC)

Therapeutic effect of Amiloride :

↓

Block Na^+ channels

① T/t of Liddle's Syndrome (↑ ENaC)
② T/t of lithium induced DI
③ T/t Aerosol — Cystic fibrosis. (Mechⁿ not known)

Mannitol — Osmotic diuretics
Site — LOH & PCT
Useful for T/t of ① Glaucoma (Given i.v.)
② Cerebral edema
③ Cisplatin toxicity.
↳ Antidote — Amifostine.
Mannitol added c cisplatin to control Nephrotoxicity.

C/I — Pulm. edema (LVF)
Cerebral Hemorrhage

S/E — Hyponatremia
Headache.

ANTIDIURETICS

- ADH (Vasopressin)

V_2 Receptor:

location → V_2 seen on medullary portion of collecting duct

Action → Water Reabsorption

• Also seen on Vascular epithelium

Action → Releasing VWF & factor VIII

Desmopressin:

- Synthetic analogue of Vasopressin acting on V_2

USES: DOC for Cranial diabetes insipidus

DOC for Nocturnal Enuresis.

Useful for Hemophilia

" " Bleeding due to deficiency of VW-factor.

V_1 Receptor:

- Seen on Vascular smooth muscle

Action → Vasoconstriction

V_1 analogues: Synthetic

Terlipressin, Felypressin, Lypressin — Useful to control esophageal varices

DOC: Octreotide

Prophylaxis DOC: Propranolol

Terlipressin added c Lignocaine to prolong the action.

Selective V_2 antagonist:

Oral — Lixivaptan, Mozavaptan, Tolavaptan — DOC for SIADH

Selective V_1 antagonist:

Relcovaptan – Useful for HTN

Nelivaptan – V1b blocker

↓

Undergo clinical trail for t/t of Anxiety.

Non-selective V_1 & V_2 antagonist:

CONIVAPTAN ($V_2 > V_1$)

↳ USE: SIADH

Given i.v.

HEMATOLOGY

Thrombolytic Agents:

MOA – Plasminogen activator ⟶ PLASMIN
(Profibrinolysin) (Fibrinolysin)

eg:
- Streptokinase
- Urokinase
- Alteplase
- Reteplase
- Tenecteplase

M/C S/E – Bleeding

Antidote of Thrombolytic drugs:

EACA (Epsilon Aminocaproic Acid)

Tranexamic acid

Aprotinin.

WARFARIN : Inhibiting vit K dependent clotting factor (II, VII, IX, X)

Protein	Half life
Factor II	72 hrs
VII	4-6 hrs
IX	24 hrs
X	44 hrs
Protein C	8 hrs
Protein S	30 hrs.

- For full benefit of warfarin occurs, wait for 3 days.
- Not used in Acute DVT
- Useful in prophylaxis of Chronic DVT.
- Normal func^{n} of Protein C → inhibiting Factor V & VIII

↑⊖ ↓

SE of warfarin → Hypercoagulation.

↓ → Dermal Necrosis.

due to Protein C inhibition. → Purple toe syndrome

Warfarin therapy:

Narrow therapeutic index (Only INR done)

Two isomers < R
S (Active)

CYP2C9 → involved in metabolism of Warfarin
Duration of action → 5 days.
It undergo Zero Order Kinetic

Warfarin: INR = Patient PT / Control PT

(N) → 2-3

Prosthetic Valve → 2.5-3.5

Long term → 1.5-1.9

C/I in Pregnancy → Teratogenic

↓

Contradi Syndrome

Fetal Chondrodysplasia Punctata.

Antidote of Warfarin —

Natural Vit K_1	Vit K_2	Vit K_3
Phytonadione	Menoquinone	Menadione

↓

Takes about 24hrs to reduction INR

For immediate hemostasis — Fresh frozen plasma (FFP)

New Oral drugs — direct IIa inhibitor

Ximelagatran (Cause severe hepatotoxicity) - Not used.

Dabigatran

New oral drugs : Direct Xa inhibitors

Apixaban

Rivaroxaban

Edoxaban

Betrixaban

Injecting Anticoagulant acting Via Antithrombin III pathway:

Heparin (inhibit Xa; IIa)
LMWH (inhibit Xa)
↳ eg: Enoxaparin
Dalteparin
Tinzaparin
Nadroparin

Other injectable drugs acting via Antithrombin III but only inhibiting Xa:
Fondaparinux
Idraparinux
Idrabiotaparinux —Antidote→ Avidin

Specific antidote for Heparin — Protamine Sulphate
It is chemical antagonism.
1mg of Protamine sulfate
↓
Neutralizes 100U of Heparin.

Direct Xa inhibitor — Otamixaban
(Undertrail)

Injectable — Direct Thrombin (IIa) inhibitor

Bivalent:	Monovalent
Hirudin	Argatroban (Biliary excretion)
Bivalirudin	Melagatran
Lepirudin	

- These drugs are used in pt. who developed Heparin induced Thrombocytopenia.

Adverse drug reac^{n} :

Heparin	Warfarin
A = Alopecia	A = Alopecia
B = Bleeding	B = Bleeding
O = Osteoporosis (Supplement Ca)	O = Oral (GI intolerance)
U = Uticaria (Hypersensitivity)	U = Dermatitis
T = Thrombocytopenia	T = Teratogenicity.
Rarely Hyperkalemia	

Monitoring :

Anti platelet drugs (Aspirin) — Prolongs BT
Heparin (Intrinsic pathway) — Prolongs aPTT
Warfarin (Extrinsic ") — Prolongs PT
LMWH — No need of monitoring
If monitor then Anti factor Xa ↓
In Renal failure & Obese pt.

ANTI PLATELETS

Drugs inhibiting Synthesis of TX-A_2 :

Selective COX-1 inhibitor — Low Dose Aspirin (50mg-160mg)

Thromboxane synthase enzyme inhibitor — DEZOXIBEN

Drugs inhibiting TX-A_2 Receptor :

IFETROBAN
SULTROBAN
DALTROBAN
LOSARTAN (ARB having Antiplatelet action)
VAPIPROST

Drugs inhibiting synthesis of TX-A_2 & blocking action of TX-A_2 receptor: Dual action
PICOTAMIDE

Newer drug: SERATRODAST (Thromboxane A_2 antagonist).

ADP ($P2Y_{12}$) blockers:
- Ticlopidine – Prodrug
- Clopidogrel – Prodrug
- Prasugrel – Prodrug
- Ticagrelor
- Cangrelor – Given i.v.

Ticlopidine – ~~Non~~ Not commonly used becoz thrombocytopenia & Hepatotoxicity.

Clopidogrel – Activated by CYP2C19.

Omiperazol should n't be given c clopidogrel.
Pantaprozol & Rabeprazol don't have drug interaction c clopidogrel.

Glycoprotein IIb/IIIa blocker:
Given i.v:
- Abciximab – Monoclonal antibody.
- Eptifibatide
- Tirofiban

PAR 1 blocker (Protease activated Receptor blocker)
- Vorapaxar
- Atopaxar.

Essential Thrombocytosis:

ANAGRELIDE → Platelet maturation inhibitor.

DOC for Sickle cell Anemia — HYDROXYURIA

↓

useful in Essential thrombocytosis.

Drug used for T/t of CCF:

Drugs inhibiting release of Renin:

- β-Blocker
- Clonidine
- Methyl dopa.

Renin inhibitors:

- Aliskiren (FDA approved)
- Remikiren
- Enakiren

ACE inhibitors:

- Captopril
- Ramipril
- Lisinopril
- Fosinopril (Renal & Bile excretion)

All ACE inhibitors are Prodrug except Captopril Lisinopril.

All ACEi are having Renal excretion.

Action → Vasodialation (Equally dilates Artery & Vein)

Useful for → HTN, CCF, MI, DM, Proteinuria, Scleroderma.

↓

Nephroprotective.

C/I – ① Pregnancy
② B/L Renal stenosis
③ Severe Hyperkalemia

Bradykinin antagonist : Icatibant
↓
Useful for angioedema & dry cough.

Hereditary angioedema:
C1-esterase inhibitor deficiency.

ICATIBANT
RUCONEST → Human Recombinant C1-esterase inhibitor
Ecallantide, Aprotinin] Kallikrein inhibitor.

DANAZOL → Antigonadotropin & anti-androgen action
(Impeded androgen)

Sampratilat, Omapatrilat] – inhibit Vasopeptidase – ACEi

Vasopeptide :

PEPTIDE

ANP · BNP · URODILANTIN

Func^{n} – Natriuresis –
Diuresis
Vasodilation

Synthetic Analogue: Carperitide, Nesiritide, Ularitide

Nesiritide:

Synthetic analogue of BNP

Action → Diuresis
Natriuresis
Vasodilation

Useful for t/t of CCF.

- Given iv, Never oral
- Metabolism → Vasopeptidase
- Shorter ~~bio~~ half life – 20 min

S/E – Severe Hypotension

Other name of Vasopeptidase – Neprilysin (Neutral endopeptidase).

Selective Vasopeptidase inhibitor:

Ecadotril
Sacubitril

Omapatrilat – inhibit Vasopeptidase, ACEi } Dual enzyme inhibitor.
Sampatrilat – inhibit Vasopeptidase, ACEi } Dual enzyme inhibitor.

ARB's:

Losartan
Valsartan
Telmisartan
Olmisartan
Azilsartan

- Indication & C/I same as ACEi.

Losartan:
Action → Uricosuric action
TXA_2 antagonism

Telmisartan
- Agonistic action on PPAR γ_2
(Peroxisome proliferator – activated receptor)
So used in T/t of DM.

Aldosterone Antagonist:
Spironolactone
Canrenone
Eplerenone
Drospirinone

ACEi + Spironolactone ⇒ Severe Hyperkalemia.
Any drug blocking RAAS pathway will cause hyperkalemia

Other drug useful for t/t of CCF
Phosphodiesterase 3 inhibitors:
Amrinone (Inamrinone)
Milrinone
Levosimendan
] Inodialator.

→ M/C S/E – Thrombocytopenia
M/C S/E of Milrinone – Arrythmia

Heart failure :-

Na^+-K^+ pump inhibitor : Digitoxine.

Direct myosin activator : Omecamtiv mecarbil
(+ve inotropic)

Calcium sensitizer :
Pimobendan
Levosimendan (PDE-3 blocker)

Disease modifying drug /
Drug reducing mortality in CCF :
β-Blocker (Carvedilol, Bisoprolol, Metoprolol)
ACEi
Angiotensin Receptor Blockers (ARBs)
Spironolactone
ISDN + Hydralazine.
↓
Isosorbide dinitrate

↳ Except these drugs, all other drugs control symptoms only in CCF.

GIT

Drug useful for Acid peptic disease (APD):

H_2 Antihistamines:

- Cimetidine – Least potent.
- Ranitidine
- Famotidine – Most potent
- Roxatidine
- Nizatidine
- Loxalidine.

↳ Basal acid output & Nocturnal (more effective)
So, give at Bedtime.

↳ Renal excretion.

Cimentidine – Antiandrogenic
CYP enzyme inhibitor
Least potent.

PPI (H^+–K^+ ATPase inhibitors):

- Omeprazole (Metabolism by CYP2C19, CYP3A4)
- Esomeprazole
- Pantoprazole
- Lansoprazole
- Rabeprazole

Short half life for less than 2hr → But acting for longer duration → Hit & Run drug
(Irreversible inhibition of Proton pump).

Omeprazole not given c clopidogrel.

Rabeprazole, Pantoprazole → No significant drug interaction (preferred c clopidogrel).

Antacids:

Sodium Bicarbonate

Calcium Carbonate – Shouldn't be taken c̄ milk

↓

bcoz Milk alkali Syndrome.

GELUSIL:

Combination of Aluminium Hydroxide (Constipation)
+ Magnesium Hydroxide (Diarrhoea)

Ulcer protective drugs:

Sucralfate (Sucrose + Sulfated Aluminium hydroxide)

- Acts only in Acid medium (pH below 4)
- It shouldn't be combine c̄ H_2 blocker/PPI/ antacid.

Bismuth

- Black stool & tongue.

C/I – Renal failure.

Ulcer healing drugs:

Carbenoloxone

↳ S/E – Displaces aldosterone from protein binding.

Prokinetic drugs:

Drugs promoting GI motility.

D_2 antagonist:

Domperidone

Metaclopramide

5HT4 agonist :

Cisapride, Mozapride, Tegaserod, Iveosulpride — Cause QT prolongation ∴ Withdraw

Cholinergic agonist (M3 agonist)

Bethanechol

Neostigmine.

5HT3 blocker :

Ondansetron.

Antibiotic having Prokinetic action : Macrolide.

↓

acting on motilin receptor of small intestine cause diarrhoea.

Among Macrolide — max^m Prokinetic

Erythromycin

Drug used in Anticancer / Radiation — drug induced vomitting

5HT3 antagonists :

Ondansetron M/C S/E — Headache.

Granisetron

Tropisetron

Dolasetron → QT prolongation

Palonosetron → Highly selective 5HT3 antagonist

Long acting ($T_{1/2}$ = 40hrs)

Supportive drug : For better efficacy

Ondasetron / mixed ☆ → D2 blocker, BZD, Steroids

- D2 blocker → Domperidone
- Steroids → Dexamethasone, Methyl prednisolone.

Antiemetic belonging to Cannabinoids

Nabilone, Dronabinol — Antiemetic + Apetite stimulant.

2-3 days after Chemotherapy → Late phase Vomitting

T/t → ① Aprepitant (oral)
② Fos aprepitant (i.v.)

↓

Neurokinin 1 antagonist

③ Palonosetron.

IBS

T/t of Constipation dominant IBS:

Magnesium hydroxide
Methyl cellulose
Lactulose syrup. → Also useful for Hepatic encephalopathy.

Tegaserod, Prucalopride — 5HT4 agonist

Lubiprostone
→ ClC-2 (Type-2 chloride channel activator)

Linaclotide (Guanylate-cyclase-C activator)
↳ Cystic Fibrosis transmembrane conductance regulator Activator (CFTR activator)

↓

Crofelemer — Inhibitor of CFTR
↳ USE — HIV drug induced diarrhea.

Antibiotic used for t/t of constipation in IBS:
Neomycin (Orally) → For t/t of Hepatic encephalopathy
Rifaximin → Pre-op Bowel Sterlization
Probiotics.

Rifaximin:
Useful for — ① IBS
② Hepatic encephalopathy
③ Traveller's diarrhea
④ Pseudomembranous colitis.

For t/t of opioid induced constipation:
Methyl nalltrexone (S/c)
Alvemopan (oral)

Diarrhea in IBS:
5HT3 antagonist for t/t of diarrhoea in IBS:
Aloselron
Ramoselron
Cilanselron

Aloselron — Rarely cause dangerous problem
It cause Ischemic colitis
↳ So withdrawn

- But if use - give c great caution & Informed consent.
- Only in female

Other drugs for diarrhoea:
Cholestyramine resin

Opioid for diarrhoea:
Loperamide
Diphenoxylate + Atropine ⇒ Control addiction.
Codeine.

For t/t Abdominal pain:
Anticholinergic drugs] Muscle relaxant property.
Imipramine]

Cholecystokinin antagonist:
Lorglumide, Loxiglumide > Inhibits GI motility
↓
Useful for IBS (diarrhoea)

BRONCHIAL ASTHMA.

Methyl Xanthines — Aminophylline, Theophylline > Bronchodilator.

MAO — Adenosine antagonism — lead to seizure.
Non-selective PDE inhibition

Side effect	Proposed mechanism
Nausea & Vomiting, Headaches, Gastric discomfort	→ PDE4 inhibition
Diuresis, Epileptic seizures	→ A_1 receptor antagonism
Cardiac arrhythmias	→ PDE3 inhibition, A_1 receptor antagonism.

M3 Blocker, β_2 agonist > Bronchodilators
M/c for acute Asthma

Leukotriene antagonists:

Arachidonic Acid
↓ 5 lipooxygenase
LTA_4

LTB_4 → BLT Receptor

LTC_4 → LTD_4 → LTE_4
(Cysteine LT_2 Receptor)
(Cysteine LT_1 Receptor)

Lipooxygenase Inhibitor
Zileuton
↳ Not used bcoz Hepatitis.

Leukotriene antagonist:
Zafirlukast
Montelukast
Pranlukast

Chronic therapy cause — Churg strauss Syndrome
↓
Headache
Eosinophilia
Vasculitis.
↓
For t/t : MEPOLIZUMAB
(IL-5 antagonist)

Mast cell stabilizers:
Sodium chromoglycate
Nedocromil
Ketotifen (Additional Antihistaminic property)

Monoclonal antibodies:
Omalizumab → IgE antibody agonist.
↳ S/c, Hypersensitivity.

Newer drug — Reslizumab
Mepolizumab (IL 5 antagonist)

PDE inhibitors:

PDE inhibitors		
Methyl xanthines	PDE I, II, III, IV	Asthma
Cilomilast, Roflumilast	PDE IV	Asthma
Apremilast	PDE IV	Active Psoriatic aethritis
Amirinone, Milrinone	PDE III	CCF
Sildenafil, Verdenafil, Tadalafil	PDE V	Erectile dysfunction
Pentoxyphylline	Non-selective	PVD
Cilastazol	PDE III	PVD
Vinpocetine	PDE1, Vasodilator	Parkinson, Alzheimer's ds.

EXPECTORANTS

Mucolytics:
- Carbocysteine
- Methyl cysteine
- Erdosteine
- Bromohexane
- Dorsane alpha
- N-acetyl cysteine.

Cough suppressant:
- Codeine
- Phol codeine
- Dextromethorphan.

Antihistamines

1st Generation

→ Antihistaminic + Anti cholinergic action

USE : Allergic cond^{n}
Insect bite
EPS
Motion sickness

1 Generation drugs :

CPM (chlorpheniramine Maleate)
Promethazine (Most sedative, Highest anticholinergic)
Diphenhydramine
Cyclizine
Meclizine (Useful for Sea sickness)
Cyproheptadine (Antihistaminic + Anticholinergic + Antiseritonergic action)
↓
Appetizer, Useful in migrane
Cause Serotonin Syndrome.
Hydroxyzine (Antihistamine + Anti-anxiety)
↳ produces metabolite – Cetrizine.
Doxepin → Given topically (for itching)
↳ TCA – Atopic dermatitis, Lichen simplex
Cinnarizine (H_1 + M + 5HT2)
↳ Use in Vertigo
↑
Betahistine (Histaminergic drug)

2nd Generation

2nd Generation drugs:

Terfenadine, Astemazole – Causes QT prolongation → Withdrawn

Metabolite → Ebastine → Still available

Fexofenadrine

Cetirizine (Metabolite of Hydroxyzine)

Levocetirizine

Azelastine (Maximum topical, nasal spray)

Mezlastine

Acrivastin

Active form → Loratidine (longest) → Desloratidine

Rupatidine (Platelet activating factor antagonism)

↓

Lexipafent, Apafaint → For t/t of Acute Pancreatitis

Topical antihistamines:

Azelastine – Nasal spray

Olopatadine – Nasal spray, Ophthalmic drop, Oral

↓

Mast cell stabilizing

Alcaftadine, Epinastine – Eye drop.

H3 antagonist / inverse agonist:

Pitolisant (Tiprolisant) → Orphan drug.

↳ T/t of Narcolepsy

Prostaglandins

PGE_1:

Misoprostol:
- Useful for T/t gastric ulcer (NSAID induced)
- Used for abortion
- Teratogenicity → Mobeious Syndrome

Alprostadil
- Vasodilator
- Useful for Erectile dysfunc^n (Given injectable)
- Useful for maintain patency of ductus arteriosus.

PGE2:

Dinoprostone
↳ Uterine contracting agent
Useful for abortion.

Enprostil, Rioprostil
- Useful for t/t of Gastric ulcer.

PGF2α:

Carboprost
↳ USE: Post partum Hemorrhage (PPH)

Dinoprost
↳ USE: Uterine contracting agent for abortion.

Latenoprost, Bimatoprost, Travoprost, Unoprostone
- Useful for Glaucoma
  ↓
  By promoting drainage via Uveoscleral route.

Cause Iris pigmentation

Causes Hypertrichoses of eyelash

PGI_2 : Prostacyclin

Epoprostenol
Treprostinil
Beroprost
Iloprost
} – Useful for 1° pulm. HTN

Drug used for 1° pulm HTN:

① Inhaled NO – Vasodilator
② CCB (Nifedipine, Diltiazem)
③ PDE5 blockers → Sildenafil, Tadalafil.
④ Endothelin receptor blocker (ERBi) → Bosentan
Ambresentan
Macitentan
} Hepatotoxic
⑤ Direct guanylate cyclase inhibitor → Riociguat
Chinociguat.
⑥ PGI_2 → Epoprostenol
Treprostinil
Beroprost
Iloprost.
⑦ New drug → Selexipag (Prostacyclin receptor agonist)
↳ Useful for t/t of 1° pulm HTN.
⑧ Rho kinase inhibitor → Fasudil

NSAID

Blocks both

COX-1 COX-2

Aspirin:

- Analgesic
- Anti pyretic action
- Anti inflammatory

— All are property of all NSAID.

Prevent Colonic & rectal cancer

Aspirin + Nicotinic acid ⇒ Prevent flushing.

C/I — in t/t viral fever in children < 12yrs.

↓

Cause Reye's syndrome.

- Liver damage
- Encephalopathy
- Febrile illness

M/C S/E of Aspirin & other NSAID:

- Gastric ulcer.

Non-selective COX inhibitor

Indomethacin — Anti inflammatory

Use:
- Frontal headache
- Closure of ductus arteriosus
- Batter's syndrome

Phenylbutazone
- may cause bone marrow ~~depression~~ suppression.

Ibuprofen - Safe in children

Mefenamic acid - Useful in dysmenorrhoea.

Piroxicam - longest acting NSAID.

Preferable COX2 inhibitor:
- Nimuselide
  ↳ Cause severe hepatotoxity in children (Unsafe)
- Nabumetone
- Etodolac
- Meloxicam

Highly selective COX-2 inhibitor:
- Rofecoxib
- Celecoxib
- Valedecoxib
- Etoricoxib
- Parecoxib
- Lumiracoxib.

] Risk of developing HTN & CCF

COX-3 blocker
Paracetamol
Overdose ↳ Causes liver toxicity.

Other analgesic: Other than NSAID & opioids.
Ziconotide (Conotoxin)
- N type CCB
- Intrathecal given

For anti inflammatory action of Aspirin → 300 - 400mg
aspirin required ≤ cause Turic acid.
& > 2gm → Gastric perforation.

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Nefopam – Amine uptake inhibitor
Na^+ channel blocker

Salivex – Cannabinoid
↳ use – Cancer pain

~~Eno~~ Entonox – $N_2O + O_2$
↳ for painless labour.

Drug useful for t/t of Gout:

Acute Gout:
Give NSAID or, Steroids or, colchicine

Cholchicine → Acting by disruption of microtubule
↓
Neutrophil drunken walk.
S/E – Diarrhoea (Bloody)
Unsafe in RF

NSAIDs → Naprexen
Indomethacin
Sulindac
Aspirin is C/I for gouty arthritis.

Drug used for chronic gout:
Xanthine oxidase inhibitor:
Allopurinol
Febuxosat.
6-Mercaptopurine.

Uricosurics:

Probenacid (Unsafe in RF)
Sulfinpyrazone
Benzbromarone
Lesinurad.

Other drug having uricosuric actions are –
Losartan
Fenofibrate
Amlodipine

Newer drug :–

For aggressive control of Gouty arthritis
↳ Give intravenously
- Rasburicase] cause Rapid metabolism
- Pegloticase] of uric acid.

Newer drug for T/t of RA :

Normal – cytokine balance

Pro-inflammatory Cytokines = Anti-inflammatory cytokines.

↓

TNFα, IL-1, IL-6

TNF α blocker :

Immuno suppressant
- Infliximab (i.v)
- Etanercept (S/C)
- Adalimumab (S/C)
- Golimumab (S/C)
- Certolizumab (S/C)

Test
Before giving TNFα blocker TB should be ruled out.
-PPD test
↳ Purified Protein derivative skin test

- All are unsafe in Hepatitis B virus infected pt.

Analogue of Interleukin 1 (IL-1) Receptor Antagonist:
ANAKINRA

IL-6 blocker:
Tocilizumab
Sarilumab

Newer drug – Rituximab (CD20 receptor antagonist)
↳ Cause PML (Progressive Multifocal Leucoence-phalopathy.

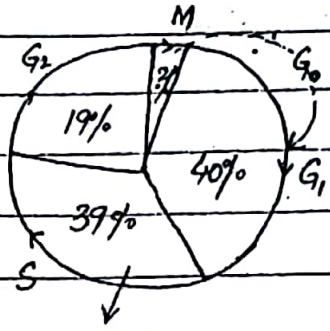
Abatacept, Belatacept → Targeting against CD80/86 Receptor
↳ USE – RA

Tofacitinib – JAK 1 & 3 blocker
↳ USE – RA.

Leflunomide
↳ Inhibit dihydro orotate dehydrogenase
S/E – Hepatotoxic
C/I – Pregnancy.

ANTI CANCER DRUGS

Cell cycle:



G_1 (40%) → Minor development take place.

S-phase → DNA synthesis
(39%) By < Topoisomerase II enzyme
Folic acid, Purine, Pyrimidine.

G_2 (19%) → Extra development take place.
By Topoisomerase

M (2%) → Multiplication

Drugs acting on G_1 phase:
L-Asparaginase (enzyme)
Steroids

L-Asparagine – Origin from E.Coli (Naturally occuring)
– Useful for ALL
S/E – Hemorrhagic pancreatitis
Hypercoagulation
No significant Myelosappression.

Thromboembolic Complications.

Drugs acting on S-phase:
Anti metabolites
Epi podo phyllo toxins
eg: ETOPOSIDE
TENEPOSIDE

Drugs acting on G_2 phase: Topoisomerase-I inhibitor.
Camptothecins < IRINOTECAN – cholino mimetic property.
TOPOTECAN ↓
SE – Diarrhoea.
(dose related toxicity)

Bleomycin (Anticancer + Antibiotic)

– All anticancer + antibiotics are C-cycle non-specific except Bleomycin.

Drug inhibiting mitosis:
Vinka alkaloids – Vinblastin, Vincristine, Vinorelbine] plant origin.

Taxanes – Paclitaxel
Docetaxel
Cabazitaxel.

Newer drug – Ixabepilone, Eribulin > Useful for Breast Ca.

For HER2 +ve Breast Ca – TRASTUZUMAB
For Rx HER1 & HER2 – TK Blocker – LAPATINIB.

Newer drugs in cancer therapy:

Tyrosine Kinase inhibitor (TKi's):

Tyrosine Kinase Receptor – EGFR (HER-1)
VGFR
PDGFR

TKi's acting EGFR blocker:

Gefitinib, Erlotinib, Afatinib – Useful for t/t of Metastatic Small cell lung Ca.
↳ Also useful for Pancreatic Ca.
↓
DOC: Gemcitabine

S/E – Dysmorphic eyelashes (Erlotinib)

VGFR blocker:

Sorafenib – Useful for RCC, HCC
Sunitinib – Useful for RCC, GIST
Lenvatinib – Useful for DTC

PDGFR blocker

Imatinib – DOC for CML
↑ 1st gen. TKi
Useful for GIST (C-kit)
↓
due to alteration of c-kit – Resistance
↓ T/t of Resistance CML
DASATINIB, NILOTINIB – 2nd gen. TKi

Multi-targeted TKi:

Vandetanib – Useful for Medullary Ca Thyroid.
↳ Target against EGFR & VGFR.
Axitinib, Pazopanib – Targeting against VGFR & PDGFR
Useful for RCC

TRASTUZUMAB → For HER-2 +ve Breast Ca.

LAPATINIB → Against HER-1 & 2 +ve Breast Ca.

All the TKi are taken orally.

Common S/E – GI toxicity
(Nausea, Vomitting, Diarrhoea)

Any drug block EGFR causes HTN.

Monoclonal antibodies (MABs)

TRAS (TU) (ZU) (MAB)

Target Source

TU = Tumor Zu – Humanised

Li = lowering immunity Xi – Chimerical (Non human eg Mice)

Ci = Target circulation.

Vi = Virus.

BASILIXIMAB – Target against IL-2

ABCIXIMAB – Target against GP2B3A.

PALIVIZUMAB – Target against RSV.

Trastuzumab –

Target against HER-2 receptor

Useful for HER-2 +ve Breast Ca.

Most of MAB given by i.v. infusion

Specific S/E → Cardiomyopathy

Infusion reaction.

Rituximab :

Target against CD20 on B-cell.
Useful for B-cell lymphoma
Other uses : C = CLL
H = Hemolytic anemia
I = Idopathic thrombocytic Purpura (ITP)
N = NHL (Non-hodgkin Lymphoma)
A = Arthritis (RA)
Myasthenia Gravis.

M/C S/E – PML

Bevacizumab : Target circulation.

Target against VGFR
Useful for Metastatic colorectal CA (iv)
↓
M/C → 5FU
Useful for RCC & Diabetic Retinopathy.
↓ ↓
i.v. Intravitreous

S/E – HTN

Newer drug : RAMUCIRUMAB

- Target against VGFR
- Useful for Gastric Cancer.

BRENTUXIMAB

- Target against CD30 on B cell.
- Useful for Hodgkin lymphoma.

Omalizumab – Target against IgE → USE: Bronchial Asthma (BA)

Resilzumab, Mepolizumab – Target against IL5 → USE: BA

Denozumab – Target against RANK-L → Osteoporosis.

Eculizumab – Target against C5 → Paroxysmal nocturnal hemoglobinuria.

Evolocumab, Alirocumab – Target against PCSK9 → Lipid lowering.

Ibalizumab – Target against HIV (entry inhibitor)

Macular degeneration (MD)

Dry type	Wet type
less blood supply	Age related MD (ARMD)

Drugs useful for Wet type MD:

Photodynamic therapy

VERTEPORFIN – i.v.

VEGF inhibitor:

Bevacizumab, Ranibizumab, pegaptanib, Aflibercept – Intravitreal inj.

Drug for Vitreomacular degeneration :
Ocriplasmin (Newer drug).

Bull's eye Retinopathy – Caused by chloroquine.
Crystalline Maculopathy – Caused by Tamoxifen.
Field of Vision defect – Vigabatrin.
Whorl-like pattern – Already done.

Kayser-Fleischer ring – Wilson's ds (Ceruloplasmin deficiency).

Chelating Agents.

Metal	T/t
Copper	Penicillamine (SLE, optic Neuritis)
	Trientine
	Zinc sulphate (Safest)
	Potassium Sulfide
Hepatitis or cirrhosis c decompensation	Zinc
Mild – Moderate hepatic decompensation	Trientine + Zn
Neurological or Psychiatric Symptom	Tetrathiomolybdate + Zn.
For maintanence in pregnancy & Children	Zinc

Metal	T/t	
Lead	BAL	C/I in Iron & Cadmium poisoning.
Arsenic	BAL	
Mercury	BAL	
Iron	Desferrioxamine Deferiprone Dexrazoxane.	

DOXORUBICIN

S/E - Cardiomyopathy

Antidote for Doxorubicin poisoning — Dexrazoxone.

Anti-metabolites:

Anti cancer + Immunosuppressive.

Drug acting against folic acid:

Methotrexate

Pemetrexate } - Useful for Mesothelioma
Trimetrexate } NSCLC

Pralatrexate. - For T-cell lymphoma.

Methotrexate:

(N) DHFA $\xrightarrow{DHFR}$ THFA

MAO: Methotrexate actively penetrate into cancer cell it inhibit DHFR, Ultimately inhibiting DNA synthesis, So stop S-phase of cell cycle.

Resistance due to alteration/mutation of DHFR.

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Specific antidote — Folinic acid or Leucovorin
antagonist.

Folinic acid can't be given in Renal failure.

GLUCARPIDASE — Newer drug useful for t/t of Methotrexate toxicity in a pt c impaired kidney func^{n}.

USES of MTx : Anticancer :
DOC for Choriocarcinoma.
Useful for Osteosarcoma

Immunosuppressant :
RA (DMARD, low dose 7.5 mg/wk)
Psoriasis ↓
long term therapy.

C = Chorio CA
A = Abortion
N = NHL
C = Chron's ds
E = Ectopic pregnancy
R = RA.

S/E — Myelosuppression (M/C)
Alopecia
Mucosal damage. (GI toxicity)
Liver damage (on chronic therapy — in RA)
↳ Undergo LFT
Crystaluria
↳ TT — Hydration & Alkalinization

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Antibiotic causing Crystal
- Ciprofloxacin (Alkaline)
- Sulfonamide (Acidic)

Antiviral causing Crystal
- Indinavir → HIV
- Acyclovir

C/I of MTx — Pregnancy.

Purine Anti metabolites:
- 6-Thioguanine
- 6-Mercaptopurine
- Fludarabine → DOC: CLL — Useful for Hairy cell Leukemia
- Cladribine → DOC — Hairy cell Likemia (also useful for Multiple Sclerosis.)
- Pentostatin → Inhibiting Adenosine deaminase.

6-Mercaptopurine:

6-Mercaptopurine
↓ HGPRT enzyme.
6-Thiosinic Acid

Cause of Resistance — Deficiency of HGPRT enzyme (Lesch-Nyhan Syndrome)

6-MP normally undergoes evacuation (metabolism) by HGPRT.

If we give Xanthine oxidase inhibitor — ↑ plasma level of 6MP.

When we give Allopurinol ∈ 6MP reduce the dose 50-75% of 6MP.

INFα – USE: HBV, HCV
INFγ – USE: Chr. granulomatous ds.
↳ Immunostimulant.

Drugs useful for Multiple Sclerosis (MS):

Disease modifying drugs:

- Interferon Beta 1A & 1B
  - Glatiramer Acetate
  - Natalizumab (α4β1 integrin) (i.v. once in month)
    - ↓ cause PML
  - Acrelizumab (anti CD20)
  - Alemtuzumab (Anti CD52)

Mitoxantrone (Anti cancer + Antibiotic)
↳ Cause Cardiotoxicity.

Fingolimod (oral)
↳ Cause Bradycardia.

Dalfampridine (oral)
↳ Useful for Lambert Eaton Syndrome.
↳ Useful in MS in improving walking.

Cladribine (oral)

Teriflunomide (oral)
↳ derivative of Leflunomide
↳ Di-hydro orotate ....
↳ Useful in pregnancy & MS

Dimethyl fumerate.

Pyramidine Antimetabolites:

Cytarabine (Cytosine arabinoside)
↳ Cause Cerebellar ataxia.

5FU
↳ M/c use – Colorectal cancer
• Given c Levamisole

Floxuridine

Gemcitabine (DOC for Pancreatic CA)

Capacitabine. (Cause Hand foot Syndrome)

Gemcitabin — Myelosuppression
Flu like symptom
Very potent Radio sensitizer.
DOC for Pancreatic CA

Drug causing Hand foot Syndrome:
Capecitabine
5-FU
Doxorubicin
IL-2
Pemelexed.

Anti cancer Antibiotics:
Actinomycin D (Dactinomycin)
↳ Causes Radiation recall phenomenon.

Daunorubicin
Broadest Spectrum → Doxorubicin
Mitoxantrone
— Anthracyclines
Inhibit Topoisomerase II
↳ may cause Blue colour fingernails, sclera & urine.

Mitomycin
Bleomycin
Mithramycin (Plicamycin)
↳ Useful for Hypercalcemia.

Doxorubicin:
- Causes dilated Cardiomyopathy (DCMP)
- Doxorubicin in presence of Iron form free radical injured myocardium.

T/t — Dexrazoxane + Alpha tocopherol (Vit E)
↓ Iron chelator
↳ Antioxidant

Mitomycin:

- Useful for Urinary bladder Ca.
  - Usually Intravesical therapy: BCG
  - For BCG resistance — Mitomycin
    Valrubicin
- Useful for laryngotracheal stenosis.
  due to Antifibroblastic action.

Bleomycin:

Cell cycle specific acting on G_2 phase of Cell cycle.
M/c S/E — Pulm. fibrosis.

Bleomycin hydrolase is not seen in lung.
↓
so large accumulation of Bleomycin in lung.

Type I pneumocytes — Necrosis / destruction
Type II " — Hyperplasia / Metaplasia.

Anticancer drug ↓ No severe myelosuppression:

Vincristine → Cause Peripheral neuropathy.
Bleomycin
Asparaginase —Cause→ Pancreatitis
Hypercoagulation

Alkylating agents.

Busulfan

Nitrosoureas → Lomustine, Semustine, Carmustine → Delayed Myelosuppression last.
- Highly lipid soluble → Useful for Brain Tumor

Temozolamide → also for Malignant Melanoma.

Streptozocin (Chemical Pancreatectomy).

Chlorambucil (USE: CLL)

Cyclophosphamide, Ifosfamide

Melphalan (Use for Multiple myeloma)

Procarbazine, Dacarbazine.

Thiotepa

Mechlorethamine.
- ↳ Cause skin Vesicant

Procarbazine –
- Disulfiram like reac^{n}
- Among the alkylating agent Procarbazine & Melphalan cause Secondary Cancer.
  - Cyclophosphamide – less Secondary cancer.
- MAO inhibitory action

Drugs for Multiple myeloma:
- Melphalan
- Thalidomide
- Lenolidomide
- Bortezomid (Proteosome inhibitor)
  - ↳ DOC

– Punch out lesion.

Cyclophosphamide (Anticancer + Immunosuppressive):
- Prodrug.
In liver it forms Aldophosphamide
↓
Phosphoramide mustard + Acrolein (Toxic)

DOC for Wegner's granulomatosis.
M/C S/E - Hemorrhagic cystitis
↳ Due to Acrolein
Antidote - MESNA
Supportive drug - Formalin
↳ N acetyl cysteine
Carboprost (PGF2α agonist)
↳ USE:
↳ Paracetamol poisoning
Radiocontrast
Nephrotoxicity
Mucolytic

Cyclophosphamide cause ↳ SIADH
Cardiotoxicity.

Ifosfamide:
Active form - Acrolein
↓ Antidote
MESNA

Drug of C/I in Malignant Melanoma - LEVODOPA

Drugs for Multiple myeloma :
- Temozolamide
- BRAF V600E inhibitor — Vemurafenib
Dabrafenib
Trametinib

Newer drug. — Nivolumab
Ipilimumab

Aldesleukin - IL2
↳ USE : RCC, Multiple Myeloma.

Busulfan :
Used for CML
S/E — Pulm. fibrosis
Adrenal insufficiency. (Addison's ds)
↳ Hyperpigmentation.

All alkylating agent action — N7 Guanine Residue
All " " are cell cycle non specific.

S/E of Alkylating agent — Veno occlusive ds of liver.
(Budd chiari Syndrome
↓
Minimised by DEFIBROTIDE

- Permanent sterility

Least emetogenic – Vincristin
Chloroambucil

Cisplatin:
Highest emetogenic
S/E – Ototoxicity
Nephrotoxicity (dose limiting toxicity)
Neurotoxicity

Antidote – Amifostine.

Carboplatin:
S/E – Myelosuppression

Oxaliplatin:
S/E – Neurotoxicity
Pharyngeal paraesthesia.

Vincristine:
S/E – Peripheral neuropathy. (Sensory & motor).
SIADH
Vesicant.

Advantage – less myelosuppressant
less nausea.

Vinblastine:
- Myelosuppression

Taxane (Paclitaxal, Docetaxal):
- Myelosuppression
- Peripheral neuropathy (Glove & SOCK Neuropathy
- Allergy.

Role of hormones in cancer:
For all premenopausal women c ER +ve Breast cancer
1st line choice is SERM.
If Resistance give SERD.

For postmenopausal women c ER +ve Breast cancer
give Aromatase inhibitor.

#

SERM useful for t/t of Breast Ca:
Tamoxifen
Toremifen
Doloxifen
Raloxifene.

Tamoxifen –
Antagonistic action only on ER of Breast → Useful for t/t ER +ve Breast Ca.

Agonistic action on blood vessel

ADR – Hot flushes
Endometrial cancer
DVT

Raloxifene :

Antagonistic action on Breast → So use in Breast Ca.
" " " Uterus

S/E – Flushing
DVT
Not cause Endometrial CA.

Aromatase Inhibitors :

Aminoglutethimide (Chemical adrenalectomy)
Formestane
Exemestane
Vorozole
Fadrozole
Letrozole
Anastrazole.

Extra information :

SERMs for DUB : Ormeloxifene
(Centchroman)
-Use as Contraceptive pill.
Twice in wk ☐ gap of four day – First
3 month. Later once in a week.

SERMs for Dyspareunia – Ospemifene.

SERMs for induction of Ovulation – Clomiphene.

SPRM:

Ulipristal – Emergency Contraceptive (Can take 5 days after coitus)
Asoprisnil
Jelapristone – Useful in Uterine fibroid
Endometriosis

Prostatic Cancer:

Becoz of excess androgenic action.

Hypothalamus
(GnRH) – Pulsatile release
(60-120 min)
↓⊕
Pituitary
(Gonadotropins – LH/FSH)
↓⊕
Testis

FSH → Spermatogenesis ← Seminiferous cell.
LH → Leydig cell – Testosterone production
↓
overproduction cause Prostatic Ca.

Drugs ↓ Testosterone production:

(A) GnRH agonist (In continuous manner):
Leuprolide
Goserelin
Busorelin
Naferelin
Desorelin
Histrelin
Tritprelin

GnRH antagonist:
- Genirelix
- Celtorelix
- Abarelix
- Degarelix

Comparision:

Agonist	Antagonist.
Initial flare up	No initial flare up.
Histamine release	No histamine release.

↓ Testosterone cause:
- Hot flush
- Loss of libido
- Impotence
- Sarcopenia (Reduce muscle mass)
- Osteoporosis
  - t/t → Supplement Vit D
    - Bisphosphonates.
    - Denosumab.

Drugs having histamine releasing property:
- d-Tubacurarine
- Morphine
- Dexferioxamine
- Amphotericin B
- Polymyxin B
- Vancomycin. (Red Man Syndrome)

Anti androgen/:

Flutamide
Nilutamide
Bicalutamide
Enzalutamide
Cyproterone
Abiraterone.

Thalidomide:

Sedative + Anti emetic
S/E – Phocomelia
C/I – Pregnancy.
Category X!

– It has Anti cancer + Immune modulation property.
Indication: Multiple myeloma
ENL
Apthous ulcer
SLE.

Isomer { R (Therapeutic use & Teratogenicity)
S (Sedation)

M/C S/E – Constipation
Severe peripheral sensory neuropathy.

Drug	Antidote
Methotrexate	Folinic acid
Doxorubicin	Dexrazoxane
Cyclophosphamide	Mesna
Cisplatin	Amifostine.
Paliferamin	Mucositis.

Drugs useful for ↑↑ neutropenia:

Colony stimulating factor (CSF)

rG-CSF	GM-CSF
Filgrastim	Sargramostim
Pegfilgrastim	Molgramostim.
Lenograstim	

Drug useful for Anemia:
- Epoietin (Recombinant – Erythropoietin)
- Darbopoietin
- Peginesatide (Erythropoietin Receptor Stimulant)

Drug useful for Thrombocytopenia:
- Oprelvekin (IL-11)
- Thrombopoietin

Newer drug:
- Romiplostim (S/C) for ITP → by plasma exchange.
- Eltrombopag → Oral

Anti-emetic useful for Anticancer t/t :
Already done.

Immunosuppressant :
Cyclosporin
Tacrolimus (FK506)
Sirolimus
Everolimus

Drugs inhibiting synthesis of IL-2 :
Cyclosporin, Tacrolimus (FK506) > Calcineurin inhibitor.
↓
Both cause Nephrotoxicity
Tacrolimus > Cyclosporin

Tacrolimus – Macrolide compd.

Common problem – Nephrotoxicity (Dose limiting).
Neurotoxicity
Hepatotoxicity
DM
Diarrhea
Alopecia

Specific S/E of Cyclosporin – Hypertrophy of Gum
Hirsutism
HTN → T/t : Nefidipine.
Hyperkalemia

Hypokalemia — caused by → Cisplatin
Amphotericin B.

m-Tor blockers:
Sirolimus, Everolimus] -S/E - Thrombocytopenia
Hyperlipidemia (High TGL)

Azathioprine:
Purine anti metabolite
Immunosuppressant action (CMI)
No anti cancer action.

USE — RA
IBD (U. colitis)
Organ transplantation.

S/E - Myelosuppression

Azathioprine — converted in body → 6-Mercaptopurine.
↓
Metabolism by Xanthine Oxidase.

Immunostimulants:
Cytokines
Aldesleukin (Recombinant IL2) (for RCC & MM)
Interferon γ (Chronic granulomatous dz).
BCG vaccine (Intravesicle - Urinary bladder Ca)
↓
Valrubicin, Mitomycin
Laryngotracheal Stenosis

Levamisole (Anti helminthic property)
↳ Immunostimulant.

IL- modulators:

Analogues of IL-1 receptor antagonist: Anakinra
(USE-RA)

IL-3 & 4 antagonist: Pitrakinra
(USE - BA)

Analogue of IL-2: Aldesleukin
(USE - RCC, Malignant Melanoma)

IL-2 receptor blocker: Basiliximab
Daclizumab.

IL2 + Diphtheria toxin: Denileukin diftitox
↓
USE: Cutaneous T cell lymphoma.
↓
Histone deacytalase inhibitor
Vorinostat
Romidepsin.

IL-5 blocker: Resilizumab (Severe eosinophilia, BA)
Mepolizumab
↳ Hypereosinophilic syndrome
Churg strauss syndrome.

IL-6 blocker - Tocilizumab
↳ USE - RA

IL-1,6 antagonist - Steroids

Analogue for IL-11 - Oprelvikin
↳ USE - Thrompocytopenia.

IL-17 Blocker - Ixekizumab, Brodalumab } Use: Plaque Psoriasis.

IL 12 & 23 – Ustekinumab
↳ USE – [redacted] Psoriasis.

Apafant, Lexipafant (PAF Blocker) – For Acute Pancreatitis
Ivicaftor – For cystic fibrosis.
Imiquimod – For Condylomata accuminata (HPV)
Alefacept – For Psoriasis
Resiquimod – For HSV
Lu-Dotatate – For Midgut endocrine tumor.
Anagrelide – For Essential Thrombocytosis
Belimumab – For SLE
Defibrotide – For Budd Chiari Syndrome.
Hydroxyurea – For Sickle cell anemia.
Olaparib – For ovarian Cancer
• Acting by Poly ADP ribose polymerase (PARP) inhibitor.
Palbociclib, Amebaciclib, Ribociclib – For Breast Cancer
↳ CDK 4/6 (cyclin dependent kinase) inhibit
Edaravone – (Antioxidant) For ALS.

Mycophenolate mofetilate – Inhibit Inosine monophosphate dehydrogenase
(Immunosuppressant)
Pentostatin – Inhibit Adenosine deaminase.
Vorinostat – Inhibit Histone deacetylase.
Leflunomide – Inhibit dihydroorotate dehydrogenase

Toxicity caused
Cyclosporine – Nephrotoxicity
Leflunomide – Hepatotoxicity
Sirolimus – Bone marrow suppression
Azathioprine – Hypertriglyceridemia
Muromonab – Cytokine release syndrome.

ANTIMICROBIAL DRUGS

Antibiotic acting by inhibiting cell wall synthesis:

N acetyl muramic acid → N-acetyl muramic Acid peptidase.
N acetyl glucosamine →

Step 1:

The first enzyme initiating cell wall synthesis
- Alanine ligase / Racemase
  ↑⊖
  Cycloserine
  ↳ 2nd line drug of TB
  - Bacteriostatic
  S/E - Psychosis.

Step 2:

Enolpyruvate transferase ←⊖ Fosfomycin
↳ For UTI
Cause severe diarrhoea
So not in use.

Step 3:

Dephosphorylation of Bactoprenol ←⊖ Bacitracin
↓
polypeptide group of Antibiotic
USE: Wound / Ulcer healing
(Given topically)

Step 4:

Elongation of peptide chain
↳ c/c help of Transglycosylase ←⊖ Vancomycin
↓
If Alter → VRSA

Step 5:

Cross linking of elongated peptide chain

↓

by Transpeptidase ⟵ Beta Lactam
(Penicillin binding protein) (Penicillin)

↓

If altered → MRSA
(Resistance)

Antibiotics acting by inhibiting protein synthesis:

Aminoglycosides & Tetracycline binding c 30s Ribosome & inhibit protein synthesis.

Drug acting on 50s Ribosome & inhibit protein synthesis:

Chloramphenicol — Resistance due to enzyme degradation → Acetyl transferase
Linezolid

(M) = Macrolides
(L) = Lincosamides (Clindamycin)
(S) = Streptogramin.

MLS resistance → Methylation of 50s ribosomes.

Tetracycline resistance → Development of Efflux pump.

↓

Tigecycline – Resistance to efflux.

Due to enzymatic degradation → Aminoglycosides Resistance

↓

Do not develop resistance. [Amikacin
Netilmicin

All antibiotics acting by inhibiting protein synthesis are bacteriostatic exception – Aminoglycoside
Streptogramine.

Antibiotics

Penicillin:

Commercial source – Penicillium chrysogenum.

Acid Resistant: Orally.

V = Penicillin V
O = Oxacillin
D = Dicloxacillin
C = Cloxacillin
A = Ampicillin/ Amoxicillin

Penicillinase resistant:

C = Cloxacillin
O = Oxacillin (hepatitis)
N = Nafcillin (Neutropenia)
D = Dicloxacillin
U
M = Methicillin (Interstitial nephritis)

β-Lactamase inhibitor:

Clavulanic Acid + Amoxycillin
Sulbactam + Ampicillin
Tazobactam + Piperacillin

FDC (Fixed drug combination):

Same volume of distribution
or Same half life

Extended spectrum Penicillins :

Aminopenicillins → Enteroactive
- Becampicillin
- Ampicillin → Causing dirrhea due to incomplete absorption.
- Amoxicillin.

Carboxy penicillins (Enteroactive + pseudomonas)
- Carbenicillin → Cause bleeding due to disturbing platelet.
- Ticarcillin

Ureidopenicillins
(Enteroactive + pseudomonas + Klebsiella)
- Azlocillin
- Piperacillin
- Mezlocillin

Aminopenicillins are C/I in Infectious mononucleosis bcoz of risk of severe skin rash.

2nd line Anti TB C/I in HIV pt c TB : Thiacetazone
↓
may cause Steven Johnson Syndrome
↓
Skin Rash.

OCP + Ampicillin → Risk of OCP failure
↓
By interfaring OCP enterohepatic circulation.

S/E of Penicillin in syphilis pt.
↓
Jarisch herxheimer Reacn.
↓
Secondary Syphilis
No treatment
Only symptomatic — Aspirin & Sedation.

Atypical bela lactam antibiotics:
Carbapenams:
• Imipenam
- Brodest spectrum
- Shortest acting
↳ Rapidly undergo inactivation by Dehydropeptidase 1 enzyme.
↑⊖
Add Cilastatin
S/E - Seizures

• Meropenam
• Ertapenam

Monobactams:
• Aztreonam
↳ No cross reactivity.
↳ Useful for Aerobic gm +ve infection.
Similar to aminoglycosides.

for Anaerobic infection — Metronidazole
Clindamycin
↳ S/E - Pseudomembranous Colitis.

Cephalosporins.

Fourth generation drugs:

- Cefepime
- Ceftpirome
- Cefclidin

Fifth generation drugs:

Ceftobiprole Ceftaroline

→ USE – MRSA
Community Acquired Pneumonia.

Glycopeptide Antibiotics : Vancomycin
↓
t/t of Gm +ve infection.

Oral Vancomycin – Useful for Pseudomembranous colitis

i.v. Vancomycin – DOC for MRSA.

caused by Clostridium difficile.
↓
Caused by 3rd gen. Cephalosporin.

Newer drug for PMC – Rifaximin
Fidaxomicin

ADR of Vancomycin: Red Man Syndrome (M/c)
Ototoxicity
Nephrotoxicity

Other Glycopeptide antibiotics :
Teicoplanin
Oritavancin
Telavancin
Dalbavancin - longest acting (6-10 days)

Drugs used for T/t MRSA/VRSA :

VRSA → Linezolid -
S/E - Thrombocytopenia (M/C)
Optic & peripheral neuropathy.
Also used for MDR TB.
MAO inhibitory property.

VRSA → Streptogramine
Quinupristine : Dalfopristine = 70:30.
S/E - Infusion reac^{n}
Arthralgia.

VRSA → Daptomycin
↳ causing myopathy.

VRSA → Tigecycline
given i.v. tetracycline.
Resistant to efflux
Excretion - Bile
Safe in Renal failure.

Sulfonamides:

Sulfasalazine
↓ In GIT split in 2 component

Sulfa pyridine → Useful for RA.

5 amino salicylic acid. → Useful for ulcerative colitis

ADR – Allergy
Oligospermia (In male) → Infertility.

Topical – Sulfacetamide – For eye drop.
Silver sulfadiazine] – has anti-pseudomonal action
Mefanide]
↳ CA inhibitory action
↓
Metabolic acidosis.
useful for Fungal Keratomycosis.

Sulfadoxine + Pyrimethamine → For T/t of Malaria.

Toxoplasmosis:
For t/t : Sulfadiazine + Pyrimethamine + Folinic acid.

Safest drug For t/t of Toxoplasmosis in pregnancy – Spiramycin (Macrolide)

Cotrimaxazole : Sulfamethaxazole (400mg) + Trimethaprime (80mg).
Cotrimaxazole DS : Sulfamethaxazole (800mg) + Trimethaprim (160mg)
↓
DOC : Pneumocystis carinii pneumonia.

Aminoglycosides.

For t/t of TB → Streptomycin (1st line drug)
Kanamycin
Capreomycin
Amikacin
] 2nd line drug.

- All are ionised molecule so not absorbed via orally.

Streptomycin – DOC for Plague (mass prophylaxis)
↓
Doxycyclin

Also useful in – TB
Tularemia.

Aminoglycoside useful for Pseudomonas:
T = Tobramycin
A = Amikacin
G = Gentamycin

↓

Among Cephalosporin
– Ceftazidime
Cefoperazone.

For severe Pseudomonas infection – TOC is combination of Cephalosporin c Aminoglycosides.
eg: Ceftazidime + T or A or G.

Last option for severe resistance case of Pseudomonas

↓

Polymyxin B.

Paramomycin –
Oral – Amoebiasis
i.v – Kala azar.

Neomycin :
generally parentrally
Oral – Gut sterilization
Hepatic encephalopathy.

Aminoglycoside follow conc^{n} dependent killing pattern so given OD dose.

Beta Lactam follow time dependent killing so given TDS / QID.

Post antibiotic effect of Aminoglycoside :
Even though the ~~blood~~ drug level is lower than the MAC value still produce action.

Common S/E of Aminoglycoside :
Nephrotoxicity
Ototoxicity
Neuromuscular block (Neomycin)

Among the Aminoglycoside – Gentamycin, Tobramycin, Neomycin → Highly Nephrotoxic
Least Nephrotoxic – Streptomycin

Max^m deafness caused by – Kanamycin
Amikacin Max^m.
Neomycin

Deafness 1st high frequency sound → lastly low frequency sound.
First damage Base of hair cell → lastly apex of hair cell.

Vestibular damage – Streptomycin
Gentamycin.

Equal – Tobramycin
Least – Netilimycin.

Quinolones:
MOA: inhibits DNA Gyrase in Gram -ve
inhibit Topoisomerase IV in Gram +ve.

Route of Excretion – Kidney.
↳ So not given in Renal failure.

Excretion via liver – Prefloxacin
Trovafloxacin
Moxifloxacin
} Used in RF (Safe)

Ciprofloxacin:
DOC for Typhoid
↳ Currently 1st line choice
– Ceftriaxone (i.v.)
(In children/Pregnancy)
or in Ciprofloxacin Resistance.

Drug interaction ~ theophylline:
Ciprofloxacin is microsomal enzyme inhibitor, when ~~~ given ~ theophylline, theophylline level ↑ in plasma which causes convulsion/seizures.

Withdrawn Quinolones:
Trovafloxacin — liver toxicity.
Grepafloxacin — QT prolongation
Gatifloxacin — Unpredictable glucose profile.
↳ Only systemic use was withdrawn
Eye drop available.
Clinafloxacin — Phototoxic

available Quinolones. < Sparfloxacin (longest action)
Lomefloxacin

Macrolides.

Clarithromycin:
Useful for — MAC
H. pylori
Leprosy.

Azithromycin:
Useful for — MAC
Gonococci/Syphilis/Chancroid
Chlamydia
Legionella
Campylobactor jejuni

Common S/E of Microlides —
- GI toxicity → due to motilin
- Hearing impairment.
- Hepatitis
- Cholestatic jaundice caused by erythromycin estolate.
- ~~Erythromycin estolate~~

Drug interaction :
- All microlides are microsomal enzyme inhibitor

Erythromycin – Max^m microsomal enzyme inhibition so max^m drug interaction

Azithromycin – Least microsomal enzyme inhibition

Azithromycin may cause QT prolongation.

Erythromycin aggravates pyloric stenosis.

Tetracycline.

Tigecycline –
Given i.v.
Useful for MRSA/VRSA
Excreted by bile so safe in Kidney failure.

Doxycycline –
Excreted via bile, safe in RF

Demeclocycline –
Photofoxic
Cause DI
Useful for SIADH.

Minocycline :
Used for leprosy.
↳ Rifampicin
Ofloxacin
Minocycline.
S/E - Vestibulo toxicity.

All tetracycline having risk of causing elevation of ICT called Pseudotumour Cerebri.

Outdated tetracycline may cause Fanconi Syndrome.

Tetracyclines are DOC for ① Rikettesial infection
② Chlamydia infection
③ Lymphogranuloma Venerum. (LGV)

Tetracycline used as Prophylaxis of : Cholera
Brucellosis
Plague.

C/I in pregnancy - Fulminant hepatic failure
Baby < Bone & teeth problem.

Most safest antibiotics in pregnancy → β-lactam
↓
Cephalosporin & Penicillin > Azithromycin

Antibiotic & Colour association:
Grey baby – Chloramphenicol
Yellow baby – Sulfonamide
Red man Syndrome – Vancomycin
Discoloured teeth – Tetracyclines.
Coffee coloured teeth – Nitrofurantoin
Loss of Red/green perception – Ethambutol.
Reddish black – Clofazimine.

Tuberculosis

Anti-tubercular drugs:

Isoniazid (INH):
- activated by the help of INH A gene & catalase peroxidase.

MOA: Inhibiting mycolic acid synthesis.

- Undergoes metabolism by acetylation.

S/E – Hepatotoxicity (M/c)
↳ due to formation of Acetyl hydrazine
Neuropathy
↳ t/t – Slow administration of Vit B6
Prophylactically – 10mg/day
Neurotoxicity – 100mg/day.
Memory impairement
Psychosis.
Shoulder hand syndrome
SLE
Cheese Reac^{n}.

It is micro enzyme inhibitor.

Doesn't require dosage adjustment in pts c Renal disease.

Useful for prophylaxis of TB
Maxm CSF penetration.

Iproniazid → derivative of Isoniazid.
Used for elevating mood.

Rifampicin:
- Activated c help of Repo B gene.

MOA: Inhibit DNA dependendent ~~RNA~~ RNA polymerase.

- Excretion via Bile & faces
So safe in RF.

S/E - Non serious:
Reddish orange colour (Urine, Sweat & tears)
Staining of contact lenses.

Serious:
Hepatitis
Respr syndrome
Hemolysis
Purpura.

It is microsomal enzyme inducer
pt c HIV Receiving antiviral drug, if we use Rifampicin for TB, Ht failure occurs.
Alternate drug → Rifabutin → Causes Pseudo jaundice.

Pyrazinamide :
- Act by inhibiting myeolic acid synthesis.

S/E - Hepatotoxicity
Hyperurecimia

No drug interaction bcoz Neither microsomal enzyme inducer or inhibitor.

Undergoes renal route of excretion so need dosage adjustment in RF pt.

Ethambutol :
Bacteriostatic
MOA : Inhibiting Arabinoglactan synthesis.

S/E → • Optic neuritis
↳ loss of ability to differentiate red from green.
↳ Supplement c Hydroxycobalamine (Vit B12)
• Hyper urecemia.
Excretion → Undergo renal route of Excretion
- Need dose adjustment in RF pt.

Streptomycin :
C/I in pregnancy bcoz cause permanent deafness.
in Children.

TB in liver ds pt:
Avoid — Isoniazid, Rifampicin, Pyrizinamide.

Safe — Streptomycin, Ethambutol.

TB in a Renal ds pt:
Avoid — E, P, S

Safe — R > H

Newer drug for MDR-TB:
Bedaquiline:
Inhibit mycobacterial ATP synthase.
Food ↑ Absorption.
Cross resistance c clofazimine
May cause QT prolongation.
↳ Cardiotoxicity.

Delamanid
Pretomanid — Inhibit Mycolic acid synthesis.

Sutezolid — Derivative of linezolid.

Anti TB drug causing:

① Hypothyroidism — Ethionamide (also used for leprosy)
PAS

② Psychosis — INH, cycloserine.

Antibiotic useful in MAC = Azithromycin,
Clarithromycin

REC Regimen (R = Rifabutin, E = Ethambutol, C = Clarithromycin)

③ Cross BBB – INH, Pyrizinamide, Rifampicine, Cycloserine.

④ Uveitis – Rifabutin

Anti-leprosy drug.

– ATT drugs → Rifampicin
Ethionamide.

Other drug → Clofazimine
Dapsone.

Antibiotic useful for leprosy – Ofloxacin
Minocycline
Clarithromycin

Dapsone – Sulphonamide

Uses of Dapsone –
DOC for dermatitis herpatiformis.

Inj. Acedapsone (i.m) one dose acting for 3 months.

S/E – Allergy (M/C)
Hemolytic Anemia.

Clofazimine –
Bacteriostatic
Anti inflammatory property.
↓
also useful for lepra reac^{n}.

S/E – Reddish black skin discolouration
Dermatological.

Lepra Reacⁿ:

Type I – Cell mediated immunity to M. leprae.

Type IV hypersensitivity.

TOC – Prednisolone (Steroid).

Type 2 – Immune complex deposition.

Type III Hypersensitivity.

T/t – Steroids
Clofazimine
Chloroquine.

Virology.

Drugs useful for HIV:

Fusion inhibitors:

Enfuvirtide
– Given S/C

S/E → Injection site reacⁿ
Pneumonia (Rare)

CCR-5 inhibitor:

Maraviroc – FDA approved
Aplaviroc } undertrail.
Vicriviroc }

NRTI's (Nucleoside Reverse Transcriptase inhibitor):

Zidovudine (M/C)
- ↳ Myelosuppressant (Macrocytic Anemia)
- ↳ Lipodystrophy → due to mitochondrial DNA polymerase

Didanosine
- ↳ Pancreatitis

Stavudine – Worst drug.
- ↳ S/E – Severe Neuropathy
  - Lactic acidosis
  - Lipodystrophy

Abacavir (Rule out HLA-B5701 allele, MI, Safe in RF)

Zalcitabine

also useful for HBV:
- Lamivudein – Best drug (No serious adverse effect)
- Emtricitabine
- Tenofovir – Causes GIT toxicity, Fanconi's Syndrome).
  - ↳ Really a nucleotide inhibitor.

NNRTI:

1st generation:
- Efavirenz
- Nevirapine, NVP
- Delavirdine.

2nd gen:
- Etravirine
- Rilpivirine.

Common S/E – Skin Rash
- Steven Jhonson Syndrome
- Toxic epidermal necrolysis.

Nevirapine
↳ S/E – Hepatitis (LFT)

Efavirenz
↳ S/E – Neuropsychosis

Integrase inhibitor:
Raltegravir
Elvitegravir } Best drug.
Dolutegravir

Protease inhibitor:
Saquinavir – Best tolerated
Indinavir – Nephrolithiasis
Nelfinavir
Ritonavir – Powerful microsomal enzyme inhibitor (CYP3A4)
↓
Called Booster.
Amprenavir
Fosamprenavir
Atazanavir → Not cause lipodystrophy.
Lopinavir.
Tipranavir → may cause intracranial hemorrhage.
Darunavir } Sulfonamide

Common S/E – Hyperglycemia
Fat redistribution
Hyperlipidemia.

TESAMORELIN – GHRF
↳ Reduce abdominal fat in HIV c lipodystrophy.

CROFELEMER – CFTR inhibitor
Use – HIV drug induced diarrhoea.

Maturation inhibitor.
- Bevirimat. (Under Trail)

HAART / CART (Highly active anti retroviral therapy):
2NRTI + 1 NNRTI
NRTI + NNRTI + PI
] Triple drug therapy
↓
To prevent drug resistance.

NACO 2011 → Zidovudine + Lamivudine + Nevirapine.

CMV (Cyto megalo Virus) → Cause Retinitis.
- Ganciclovir (DOC)
↳ M/c S/E – Myelosuppression.
Valganciclovir
Fomevirsin
Foscarnet
Cidofovir
Maribavir.

Foscarnet :–
Useful for HSV (resistant to Acyclovir)
CMV (Ganciclovir resistance)
ADR – ARF
Penile ulcer.

Cidofovir — Useful for Respr papillomatosis.

Drug for Herpes simplex Virus

Acyclovir — For HSV
ADR — Acute Renal Failure

Docosanol — Viral entry inhibitor
given topically

Famciclovir — Prodrug
Active form — 6-deoxy penciclovir.

Drug useful for Hep B:
Injection are { IFN-α
PEG-INF-α

Oral agents:
1st line — Entecavir
Tenofovir (Anti HIV drug)

2nd line — Lamivudine
Adefovir
Telbivudine.

Drugs for HCV:

Commonly we give PEG INF α plus ribavirin.

Sofosbuvir – Given orally
Renal excretion
Causes Bradycardia

Other drugs –
Telaprevir
Boceprevir
Simeprevir
Grazoprevir
~~Elbasvir~~ Elbasvir

Daclatasvir
Velpatasvir
Ombitasvir

Ledipasvir
Viramidine – (Under trial)

Antifungal drugs.

- Membrane Active Antifungal Agents:

Squalene → Lanosterol → Ergosterol → Fungal cell membr

Squalene epoxidase ⊖ ← Terbenafine

14α-demethylase cyto P450 ⊖ ← Azoles

Polyene antibiotics —

Amphotericin B + Ergosterol → Forms a pore in fungal cell

↓ Act on fungal cell wall.

↓ Destroy fungus

Amphoteracin B:

Usually given as a slow iv infusion.

Very well distributed all over body / poorly distributed in CNS.

ADR — Infusion related reacn (Fever, Chills)
Nephrotoxicity (Dose limiting toxicity).
Hypokalemia
Hypomagnesimia
Anemia
Seizure.

To avoid Nephrotoxicity — Give Hydration.

Newer formulation: ABCD (Colloid dispersion)
ABLC (Lipid complex)
Liposomal AMB (For Kalazar)

↓ less systemic toxicity.

Drug interaction – Be careful while using Amphotericin B with other Nephrotoxic agents like –
Aminoglycosides
Vancomycin
Cyclosporin.

Azoles + Amphoteracin B : Mutually antagonist
↓ ↓
Inhibit Ergosterol No action ē Ergosterol.

Terbinafine – Squalene epoxidase inhibitor.

5- Flucytosine – Antimetabolite acting on fungal nucleus.

5 Flucytosine + Amphotericin B ⇒ Synergism.

Grascofulvin –
– acting by inhibiting microtubule.
– Useful for Dermatophytosis
Onychomycosis.
– Given orally.
– Microsomal enzyme inducer
– Disulfiram like reac^{n}.

Newer Antifungal – Echinocandins
eg: Caspofungin
Micafungin
Anidulafungin
MOA – Acting on β-1,3 –glucan synthase inhibitor.
Uses – Candida & Aspergillosis.

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Nikkomycin – Inhibit chitin Synthesis
Useful for Candida & Aspergillosis.

Amoebiasis

Lumen Amoebiasis
- Diloxanide furoate (Flatulance)
- Nitazoxanide
  ↳ Use in Cryptosporidiosis
- Quinodochlor → Cause Subacute myelo optic neuropathy (SMO

Tissue
- Extraintestine
- Both intestine & Extra intestine

- Iodoquinol

- Paromomycin (oral) → i.v. for Kala-azar.
- Tetracyclines

Extraintestine :
Chloroquine.

Both :
Metronidazole
Tinidazole
Secnidazole (Single dose) – M/C C/E – Nause, Vomiting
Ornidazole (Metallic taste
Satranidazole (less ● neurological ADR)
Ementine
Dehydro ementine.

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Guinea worm : For complete removal of worm
DOC – Niridazole.

Helminthiasis

Trematodes	Cestodes	Nematodes.
DOC – Praziquantel	DOC – Praziquantal	DOC – Albendazole
Except – Fasiola hepatica	Except – Echinococcus granulosa	Except – Ochocerca Volvulus
↓	Neurocysticercosis	(Ivermectin)
Triclobendazole	↓	↓
Bithional	Albendazole (hepatotoxic)	Strongyloidosis
		Scabies
		W. bancrofti
		↳ DEC.

Leishmaniasis

Kala-azar	Cutaneous	Mucocutaneous
↳ For all forms Sodium Stibogluconate		↓
(DOC) Amphotericin B (In India)	↓	
Hyperkalemia → Pentamidine (ENaC blocker)		
Paromomycin	Fluconazole	Amphotericin B.
oral [Miltefosine	Metronidazole	
oral [Sitamaquine		

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Trypnosomiasis.

African	South American.
- Sleeping sickness.	- Chagas de
T. gambience	• T. cruzi
& T. rhodesiense.	DOC – Benznidazole
	Nifurtimox.

Early heamolymphatic stage
Suramin (DOC)
Pentamidine

Late - CNS stage
Malarsoprol (DOC)
Eflornithine.

Anti-Malarial drug

Chloroquine (M/c)
↳ Very large apparant Vd of 100-1000 L/kg.

Uses:
R – Rheumatoid Arthritis
E – Extra-intestinal Amebiasis
D – DLE (Discoid lupus erythmatosus)
L – Lepra reac^{n}
I – Infectious mononucleosis
P – Photogenic reac^{n}
M – Malaria
G – Giardiasis.

– Safe in Pregnancy.

S/E → GI toxicity (Nausea & Vomitting)
CVS (Bradycardia, HTN)
Chronic therapy cause Bull's eye maculopathy.
Lives damage.

Mefloquine:
For t/t & prophylaxis of Malaria.
Long half life.
Single oral dose
S/E - Neuropsychosis.

If combine c̄ Halofen, Quinine - Risk of QT prolongation.

HALOFANTRINE, LUMEFANTRINE:
Absorption ↑ c̄ food.
Halofantrine - more cardiotoxic.

Lumefantrine + Artemether ⇒ ACT

Primaquine
- Vivax curative
In G6PD deficiency → Cause hemolytic anemia.
C/I in pregnancy.

Artemisinin:
Artesunate, Artemether, Arteether → Fast acting drug
Short acting - Recurrentence more
↓
For extending duration of action combine c̄ Mefloquine.

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Indication :

Multidrug resistance Malaria
Cerebral Malaria.
Not indicated for chemoprophylaxis of Malaria

S/E – GI toxicity (M/C)
CVS → QT prolongation, 1st degree AV block.
Hematology → Reversible Leucopenia.

WHO approved Combine therapies :

FDC = Artemether / lumefantrine
Artesunate + amodioquine
Artesunate + SP
Artesunate + Mefloquine
} ACT's

Unsafe Antimalarial drug in Pregnancy :

Halofantrine
Tetracycline / Doxycycline.
Primaquine